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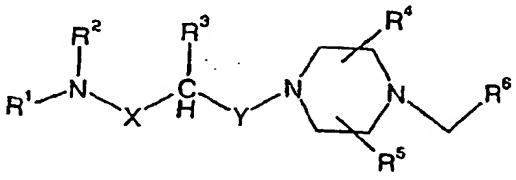
(54) Title: PIPERAZINE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS



(I)

(57) Abstract: Compounds of formula (I) wherein: R^1-R^6.X.Y are as defined in the description and salts and solvates thereof, are CCR-3 antagonists and are thus indicated to be useful in therapy.

PIPERAZINE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

This invention relates to novel compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

The primary function of leukocytes is to defend the host from invading organisms, such as bacteria and parasites. Once a tissue is injured or infected, a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction.

There is increasing evidence that the bronchial inflammation which is characteristic of asthma represents a specialised form of cell-mediated immunity, in which cytokine products, such as IL-4 and IL-5 released by T-helper 2 (Th2) lymphocytes, orchestrate the accumulation and activation of granulocytes, in particular eosinophils and to a lesser extent basophils. Through the release of cytotoxic basic proteins, pro-inflammatory mediators and oxygen radicals, eosinophils generate mucosal damage and initiate mechanisms that underlie bronchial hyperreactivity. Therefore, blocking the recruitment and activation of Th2 cells and eosinophils is likely to have anti-inflammatory properties in asthma. In addition, eosinophils have been implicated in other disease types such as rhinitis, eczema, irritable bowel syndrome and parasitic infections.

Chemokines are a large family of small proteins which are involved in trafficking and recruitment of leukocytes (for review see Luster, New Eng. J. Med., 338, 436-445 (1998)). They are released by a wide variety of cells and act to attract and activate various cell types, including eosinophils, basophils, neutrophils, macrophages, T and B lymphocytes. There are two major families of chemokines, CXC- (α) and CC- (β) chemokines, classified according to the spacing of two conserved cysteine residues near to the amino terminus of the

chemokine proteins. Chemokines bind to specific cell surface receptors belonging to the family of G-protein-coupled seven transmembrane-domain proteins (for review see Luster, 1998). Activation of chemokine receptors results in, amongst other responses, an increase in intracellular calcium, changes in cell shape, increased expression of cellular adhesion molecules, degranulation and promotion of cell migration (chemotaxis).

To date a number of CC chemokine receptors have been identified and of particular importance to the current invention is the CC-chemokine receptor-3 (CCR-3), which is predominantly expressed on eosinophils, and also on basophils, mast cells and Th2 cells. Chemokines that act at CCR-3, such as RANTES, MCP-3 and MCP-4, are known to recruit and activate eosinophils. Of particular interest are eotaxin and eotaxin-2, which specifically bind to CCR-3. The localization and function of CCR-3 chemokines indicate that they play a central role in the development of allergic diseases such as asthma. Thus, CCR-3 is specifically expressed on all the major cell types involved in inflammatory allergic responses. Chemokines that act at CCR-3 are generated in response to inflammatory stimuli and act to recruit these cell types to sites of inflammation, where they cause their activation (e.g. Griffiths et al., J. Exp. Med., 179, 881-887 (1994), Lloyd et al., J. Exp. Med., 191, 265-273 (2000)). In addition, anti-CCR-3 monoclonal antibodies completely inhibit eotaxin interaction with eosinophils (Heath, H. *et al.*, J. Clin. Invest. 99 (2), 178-184 (1997)), while an antibody for the CCR-3 specific chemokine, eotaxin, reduced both bronchial hyperreactivity and lung eosinophilia in an animal model of asthma (Gonzalo et al., J. Exp. Med., 188, 157-167 (1998). Thus, many lines of evidence indicate that antagonists at the CCR-3 receptor are very likely to be of therapeutic use for the treatment of a range of inflammatory conditions.

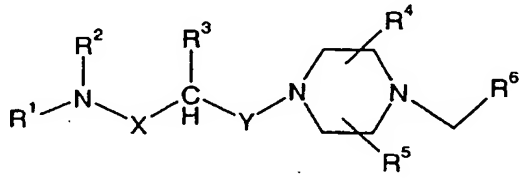
In addition to a key role in inflammatory disorders, chemokines and their receptors also play a role in infectious disease. Mammalian cytomegaloviruses, herpes viruses and pox viruses express chemokine receptor homologues, which can be activated by human CC chemokines such as RANTES and MCP-3 receptors (for review see Wells and Schwartz, Curr. Opin. Biotech., 8, 741-748, 1997). In addition, human chemokine receptors, such as CXCR-4, CCR-5 and CCR-3, can act as co-receptors for the infection of mammalian cells by microbes such as human immunodeficiency viruses (HIV). Thus, chemokine receptor antagonists, including CCR-3 antagonists, may be useful in blocking infection of CCR-3 expressing cells by HIV or in preventing the manipulation of immune cellular responses by viruses such as cytomegaloviruses.

International Patent Application publication number WO 01/24786 (Shionogi & Co. Ltd.) discloses certain aryl and heteroaryl derivatives for treating diabetes. WO 00/69830 (Torrey Pines Institute for Molecular Studies) discloses

certain diazacyclic compounds, and libraries containing them, for biological screening. WO 00/18767 (Neurogen Corporation) discloses certain piperazine derivatives as dopamine D4 receptor antagonists. United States Patent 6,031,097 and WO 99/21848 (Neurogen Corporation) discloses certain aminoisoquinoline derivatives as dopamine receptor ligands. WO 99/06384 (Recordati Industria Chimica) discloses piperazine derivatives useful for the treatment of neuromuscular dysfunction of the lower urinary tract. WO 98/56771 (Schering Aktiengesellschaft) discloses certain piperazine derivatives as anti-inflammatory agents. WO 97/47601 (Yoshitomi Pharmaceutical Industries Ltd.) discloses certain fused heterocyclic compounds as dopamine D-receptor blocking agents. WO 96/39386 (Schering Corporation) discloses certain piperidine derivatives as neurokinin antagonists. WO 96/02534 (Byk Gulden Lomberg Chemische Fabrik GmbH) discloses certain piperazine thiopyridines useful for controlling helicobacter bacteria. WO 95/32196 (Merck Sharp & Dohme Limited) discloses certain piperazine, piperidine, and tetrahydropyridine derivatives as 5-HT1D-alpha antagonists. United States Patent 5,389,635 (E.I. Du Pont de Nemours and Company) discloses certain substituted imadazoles as angiotensin-II antagonists. European Patent Application publication number 0 306 440 (Schering Aktiengesellschaft) discloses certain imidazole derivatives as cardiovascular agents.

A novel group of compounds has now been found which are CCR-3 antagonists. These compounds block the migration/chemotaxis of eosinophils and thus possess anti-inflammatory properties. These compounds are therefore of potential therapeutic benefit, especially in providing protection from eosinophil, basophil and Th2-cell-induced tissue damage in diseases where such cell types are implicated, particularly allergic diseases, including but not limited to bronchial asthma, allergic rhinitis and atopic dermatitis.

Thus, according to one aspect of the invention, there are provided compounds of formula (I):



(I)

wherein:

R^1 represents substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-8}cycloalkyl;

X and Y each independently represent a bond or $-(CH_2)_a-$, with the proviso that X and Y do not both represent a bond;

a represents 1 or 2;

R^3 represents C_{1-6}alkyl, C_{2-6}alkenyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, C_{3-8}cycloalkyl, $-CO_2R^7$, or $-CONR^7R^8$ wherein said C_{1-6}alkyl, C_{2-6}alkenyl, and C_{3-8}cycloalkyl groups may independently be either unsubstituted or substituted by one or more groups selected from $-NHSO_2R^7$, $-OCOR^7$, $-OR^7$, $-NR^7R^8$, $-NR^7COR^8$, $-NR^7CO_2R^8$, $-CO_2R^7$, $-CONR^7R^8$, $-NHCONR^7R^8$, $-SO_2NR^7R^8$, $-NR^7SO_2R^8$, $-O(CO)NR^7R^8$, $-S(O)_nR^7$, $-NHSO_2NR^7R^8$, -CN, $-NHC(=NR^{11})NR^7R^8$, C_{3-8} cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, or J groups;

n represents an integer from 0 to 2;

R^4 and R^5 each independently represent hydrogen, C_{1-6}alkyl, $-CO_2R^9$, $-CONR^9R^{10}$, oxo, or $-CH_2OR^9$;

R^6 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;

R^7 and R^8 each independently represent hydrogen, aryl, heteroaryl, C_{1-6}alkyl, or C_{3-8}cycloalkyl; wherein said C_{1-6}alkyl, or C_{3-8}cycloalkyl groups may be either unsubstituted or substituted by one or more of $-OR^{12}$, $-NR^{12}R^{13}$, $-CO_2R^{12}$, $-CONR^{12}R^{13}$, $-NHCONR^{12}R^{13}$, or aryl; alternatively R^7 and R^8 together represent a group $-(CH_2)_b-Z-(CH_2)_c-$;

b represents an integer from 0 to 4;

c represents an integer from 0 to 4;

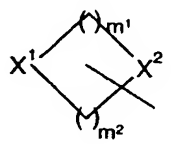
b + c is 3, 4, or 5;

R^9, R^{10}, and R^{11} may each independently represent hydrogen or C_{1-6} alkyl;

R^{12} and R^{13} may each independently represent hydrogen or C_{1-6} alkyl, wherein said C_{1-6} alkyl group may be either unsubstituted or substituted by $-OR^{14}$;

R^{14} represents hydrogen or C_{1-6} alkyl;

J represents a moiety of formula (K)



(K)

wherein;

X^1 represents oxygen, $-NR^{10}$, or sulphur;

X^2 represents CH_2, oxygen, $-NR^{10}$, or sulphur;

with the provisos that;

when moiety (K) is linked to the residue of the compound of formula (I) through an X^1 group, then X^1 represents N,

and when moiety (K) is linked to the residue of the compound of formula (I) through an X^2 group, then X^2 represents N or CH;

m^1 represents an integer from 1 to 3, m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5;

and wherein the moiety of formula (K) may be either unsubstituted or substituted by one or more of C_{1-6}alkyl, $-CONR^{12}R^{13}$, $-CO_2R^{12}$, or oxo;

Z represents oxygen, $-NR^{12}$, sulphur, or a methylene group, which methylene group may be either unsubstituted or substituted by a $-CO_2R^7$ or $-CONR^7R^8$ group;

and salts and solvates thereof;

with the proviso that N-[1-methyl-2-(4-benzylpiperazino)ethyl]aniline is excluded.

When R^1 represents substituted heteroaryl, suitable substituents include C_{1-6}alkyl, halo, nitro, aryl, and amino.

When R^3 represents substituted C_{1-6}alkyl, suitable substituents include C_{1-6}alkoxy; hydroxy; C_{1-6}alkylthio; C_{1-6}alkoxycarbonyl; C_{1-6}alkoxycarbonylamino; amino; unsubstituted aryl or aryl substituted with C_{1-6}alkoxy, amino, C_{1-6}alkylcarbonylamino, perhaloC_{1-6}alkylcarbonylamino, C_{1-6}alkylsulphonyl, C_{1-6}alkylsulphonylamino, hydroxy, or carboxy; carboxy; unsubstituted heteroaryl; arylC_{1-6}alkylaminocarbonyl; unsubstituted heterocyclylcarbonyl or heterocyclylcarbonyl substituted with C_{1-6}alkoxycarbonyl or carboxy; C_{3-8}cycloalkylaminocarbonyl; mono- and di-(C_{1-6}alkyl)aminocarbonyl; aminocarbonyl; C_{1-6}alkoxycarbonyl; C_{1-6}alkylaminocarbonyl; mono- or di-(hydroxyC_{1-6}alkyl)aminocarbonyl; C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl; hydroxyC_{1-6}alkoxyC_{1-6}alkylaminocarbonyl; aminocarbonylC_{1-6}alkylaminocarbonyl; C_{1-6}alkoxycarbonylC_{1-6}alkoxy; aminocarbonylC_{1-6}alkoxy; mono- or di-arylC_{1-6}alkyl)amino; mono- or di-(C_{1-6}alkyl)amino; C_{1-6}alkylcarbonyloxy; C_{1-6}alkylcarbonylamino; C_{1-6}alkylsulphonylamino; C_{1-6}alkoxycarbonylC_{1-6}alkyl(C_{1-6}alkyl)amino; unsubstituted arylaminocarbonyl or arylaminocarbonyl substituted with carboxy; carboxyC_{1-6}alkylaminocarbonyl; carboxyC_{1-6}alkyl(C_{1-6}alkyl)amino; C_{1-6}alkylsulphinyl; arylaminocarbonyloxy; C_{1-6}alkylaminocarbonylamino; heterocyclylamino; heteroarylC_{1-6}alkoxy; and unsubstituted heterocyclyl or heterocyclyl substituted with carboxy.

When R^3 represents substituted C_{2-6}alkenyl, suitable substituents include C_{1-6}alkoxycarbonyl.

When R^6 represents substituted aryl, suitable substituents include halo.

When R^7 or R^8 represent substituted C_{1-6}alkyl, suitable substituents include C_{1-6}alkoxycarbonyl, C_{1-6}alkoxy, unsubstituted or substituted aryl, hydroxy, hydroxyC_{1-6}alkoxy, aminocarbonyl, and carboxy.

When R^{12} or R^{13} represent substituted C_{1-6}alkyl, suitable substituents include hydroxy.

Suitable substituents for K include C_{1-6}alkoxycarbonyl, carboxy, and aminocarbonyl.

Suitable substituents for Z include C_{1-6}alkoxycarbonyl and carboxy.

Suitably, R^1 is unsubstituted or substituted heteroaryl.

More suitably, R^1 is unsubstituted or substituted benzoxazolyl, unsubstituted or substituted thienopyrimidinyl, unsubstituted or substituted pyrimidinyl, unsubstituted or substituted pyrazolopyrimidinyl, unsubstituted or substituted benzimidazolyl, unsubstituted or substituted triazinyl, or unsubstituted or substituted quinoxolinyl.

Preferably, R^1 is unsubstituted benzoxazolyl or benzoxazolyl substituted with C_{1-6}alkyl for example methyl, halo, nitro, or unsubstituted aryl for example phenyl; thienopyrimidinyl substituted with C_{1-6}alkyl for example methyl; unsubstituted benzimidazolyl or benzimidazolyl substituted with halo for example chloro, or methyl; unsubstituted quinoxalinyl or quinoxalinyl substituted with nitro; pyrazolopyrimidinyl substituted with C_{1-6}alkyl for example methyl; pyrimidinyl substituted with one or more of amino or halo for example chloro; or triazinyl substituted with halo for example chloro.

More preferably, R^1 is unsubstituted benzoxazolyl or benzoxazolyl substituted with C_{1-6}alkyl for example methyl, halo, nitro, or unsubstituted aryl for example phenyl.

Most preferably, R^1 is unsubstituted benzoxazolyl.

Suitably, R^2 is hydrogen, or C_{1-6}alkyl for example methyl.

Preferably, R^2 is hydrogen.

Suitably, R^3 is unsubstituted or substituted C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CO_2R^7$, $-CONR^7R^8$, or unsubstituted or substituted C_{2-6}alkenyl.

Preferably, R^3 is unsubstituted alkyl for example *iso*-propyl or *iso*-butyl; alkyl substituted with $-OR^7$, $-S(O)_nR^7$, $-CO_2R^7$, $-NR^7CO_2R^8$, $-NR^7R^8$, $-CONR^7R^8$, $-OCOR^7$, $-NHCOR^7$, $-NR^7SO_2R^8$, $-O(CO)NR^7R^8$, $-NHCONR^7R^8$, or unsubstituted or substituted heteroaryl; unsubstituted or substituted aryl; unsubstituted cycloalkyl; alkenyl substituted with $-CO_2R^7$; or $-CONR^7R^8$.

More preferably, R^3 is selected from the group consisting of $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, -cyclohexyl, $-(CH_2)_3CH_3$, $-CH_2OtBu$, $-CH(CH_3)OtBu$, $-CO_2Et$, $-(CH_2)_2OH$, $-(CH_2)_2SMe$, $-CH_2CO_2tBu$, $-CH_2CO_2iBu$, $-(CH_2)_3OH$, $-(CH_2)_3NHCO_2tBu$, $-(CH_2)_2CO_2tBu$, $-(CH_2)_4OH$, $-(CH_2)_4NHCO_2tBu$, $-(CH_2)_5NH_2$, $-CH_2Ph$, $-CH_2(4\text{-}OtBu)Ph$, $-CH_2(4\text{-}NH_2)Ph$, $-CH_2(4\text{-}NHCOMe)Ph$, $-CH_2(4\text{-}$

$NHCOCF_3$)Ph, -CH_2(4-SO_2Me)Ph, -$(CH_2)_2OH$, -CH_2OH, -$CH(CH_3)OH$, -$(CH_2)_3NH_2$, -$(CH_2)_4NH_2$, -$(CH_2)_2CO_2H$, -CH_2(4-OH)Ph, -CH_2(4-imidazolyl), -CH_2CO_2H, -$CONHCH_2CO_2Me$, -$CONH(CH_2)_2OMe$, -CONHiPr, -CO[1-(4-CO_2tBu)piperidinyl], -CO(4-morpholinyl), -$CONMe_2$, -CONHMe, -$CH_2CONHCH_2Ph$, -CH_2CO(4-morpholinyl), -CH_2CO(1-piperidinyl), -CH_2CONH(cyclopentyl), -CH_2CO[1-(2(S)-CO_2tBu)pyrrolidinyl], -$CH_2CONHMe$, -$CH_2CONHEt$, -CH_2CONMe_2, -$CH_2CONH(CH_2)_2OH$, -CH_2CONH_2, -$CH_2CONH(CH_2)_2CO_2$tBu, -$CH_2CONHCH_2CO_2$tBu, -$(CH_2)_2CO$(4-morpholinyl), -$(CH_2)_2CON[(CH_2)_2OH]_2$, -$(CH_2)_2CONH(CH_2)_5CO_2Me$, -$(CH_2)_2CONH(CH_2)_2OMe$, -$(CH_2)_2CONH(CH_2)_2O(CH_2)_2OH$, -$(CH_2)_2CON(iBu)_2$, -$(CH_2)_2CONHCH_2CO_2$tBu, -$(CH_2)_2CONH_2$, -$(CH_2)_2CONHMe$, -$(CH_2)_2CONMe_2$, -$(CH_2)_2CONHCH_2CONH_2$, -$CH_2OCH_2CO_2Me$, -$CH_2OEt$, -$CH_2OCH_2CONH_2$, -$(CH_2)_4NHCH_2Ph$, -$(CH_2)_4N(CH_2Ph)_2$, -$(CH_2)_4NMe_2$, -$(CH_2)_4OCOMe$, -$(CH_2)_4NHCOMe$, -$CH_2OCOMe$, -$(CH_2)_4NHSO_2Me$, -$CH_2$(4-$NHSO_2Me$)Ph, -$(CH_2)_3$[1-(4-$CONH_2$)piperidinyl], -$(CH_2)_3$[1-(4-$CO_2$tBu)piperidinyl], -$(CH_2)_3N(Me)CH_2CO_2$tBu, -$(CH_2)_4$(1-piperidinyl), (trans)-CH_2CH=$CHCO_2$tBu, -$(CH_2)_5CO_2Et$, -CH_2CONH(4-CO_2H)Ph, -$CH_2CONH(CH_2)_2CO_2H$, -$CH_2CONHCH_2CO_2H$, -CO[1-(4-CO_2H)piperidinyl], -$(CH_2)_2CONHCH_2CO_2H$, -$(CH_2)_3N(Me)CH_2CO_2H$, -$(CH_2)_3$[1-(4-CO_2H)piperidinyl], -CH_2CO[1-(2(S)-CO_2H)pyrrolidinyl], -$(CH_2)_5CO_2H$, -$(CH_2)_2S(O)Me$, -$(CH_2)_4NHCO_2Me$, -$CH_2OCONHPh$, -$(CH_2)_4NHCONHMe$, -$(CH_2)_4NH$(2-benzoxazolyl), -CH_2OCH_2(1-tetrazolyl), and-$(CH_2)_2NH_2$.

More preferably still, R^3 is selected from the group consisting of –$(CH_2)_2CO_2H$, -CH_2(4-OH)Ph, -CH_2(4-imidazolyl), -$(CH_2)_2CO$(4-morpholinyl), -$(CH_2)_2CONMe_2$, -$(CH_2)_2CONHCH_2CONH_2$.

Most preferably, R^3 is –$(CH_2)_2CO_2H$.

Suitably, R^4 is hydrogen or –$CONR^7R^8$.

Preferably, R^4 is hydrogen.

Suitably, R^5 is hydrogen, C_{1-6}alkyl for example methyl, or –$CONR^7R^8$ for example amido.

Preferably, R^5 is hydrogen.

Suitably, R^6 is unsubstituted or substituted aryl, for example phenyl.

Preferably, R^6 is phenyl substituted with halo.

More preferably, R^6 is phenyl substituted with chloro or fluoro.

More preferably still, R^6 is phenyl substituted with chloro.

Most preferably, R^6 is dichlorophenyl, especially 3,4-dichlorophenyl.

Suitably, R^7 is unsubstituted or substituted C_{1-6}alkyl, hydrogen, or unsubstituted or substituted aryl.

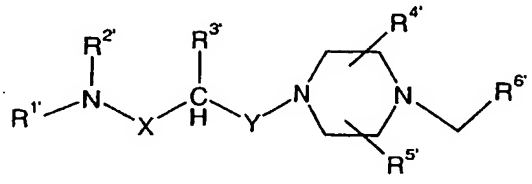
Suitably, R^8 is unsubstituted or substituted C_{1-6}alkyl, hydrogen, or unsubstituted or substituted aryl.

Suitably, R^7 and R^8 together represent a group –$(CH_2)_b$-Z-$(CH_2)_c$-.

Suitably, b is 0 or 2 and c is 2 or 3, provided that when b is 0 then Z is unsubstituted or substituted methylene.

Preferred compounds of the invention are those of Examples 58, 59, 62, 84, 93, and 94; most preferably Example 58.

There exists a preferred subgroup of compounds of formula (I) being of formula (I')



(I')

wherein;

$R^{1'}$ is unsubstituted benzoxazolyl or benzoxazolyl substituted with C_{1-6}alkyl for example methyl, halo, nitro, or unsubstituted aryl for example phenyl; thienopyrimidinyl substituted with C_{1-6}alkyl for example methyl; unsubstituted benzimidazolyl or benzimidazolyl substituted with halo for example chloro, or methyl; unsubstituted quinoxalinyl or quinoxalinyl substituted with nitro; pyrazolopyrimidinyl substituted with C_{1-6}alkyl for example methyl; pyrimidinyl substituted with one or more of amino or halo for example chloro; or triazinyl substituted with halo for example chloro;

$R^{2'}$ is hydrogen, or C_{1-6}alkyl for example methyl;

$R^{3'}$ is unsubstituted alkyl for example *iso*-propyl or *iso*-butyl; alkyl substituted with $-OR^{7'}$, $-S(O)_nR^{7'}$, $-CO_2R^{7'}$, $-NR^{7'}CO_2R^{8'}$, $-NR^{7'}R^{8'}$, $-CONR^{7'}R^{8'}$, $-OCOR^{7'}$, $-NHCOR^{7'}$, $-NR^{7'}SO_2R^{8'}$, $-O(CO)NR^{7'}R^{8'}$, $-NHCONR^{7'}R^{8'}$, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; unsubstituted or substituted aryl; unsubstituted cycloalkyl; alkenyl substituted with $-CO_2R^{7'}$; or $-CONR^{7'}R^{8'}$;

$R^{4'}$ is hydrogen or $-CONR^{7'}R^{8'}$;

$R^{5'}$ is hydrogen, C_{1-6}alkyl for example methyl, or $-CONR^{7'}R^{8'}$ for example $-CONH_2$;

$R^{6'}$ is phenyl substituted with chloro or fluoro;

$R^{7'}$ is unsubstituted or substituted C_{1-6}alkyl, hydrogen, or unsubstituted or substituted aryl;

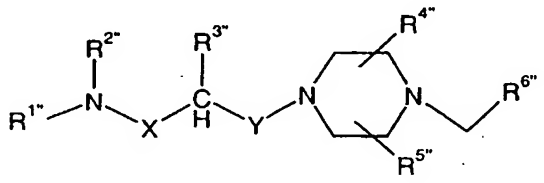
$R^{8'}$ is unsubstituted or substituted C_{1-6}alkyl, hydrogen, or unsubstituted or substituted aryl, or;

$R^{7'}$ and $R^{8'}$ together represent a group $-(CH_2)_b$-Z-$(CH_2)_c$-;

b is 0 or 2 and c is 2 or 3, provided that when b is 0 then Z is unsubstituted or substituted methylene, and ;

X and Y are as defined for formula (I) herein;
and salts and solvates thereof.

There exists a further preferred subgroup of compounds of formula (I) being of formula (I")



(I")

wherein;

$R^{1"}$ is unsubstituted benzoxazolyl or benzoxazolyl substituted with C_{1-6}alkyl for example methyl, halo, nitro, or unsubstituted aryl for example phenyl;

$R^{2"}$ is hydrogen;

$R^{3"}$ is selected from the group consisting of $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, -cyclohexyl, $-(CH_2)_3CH_3$, $-CH_2OtBu$, $-CH(CH_3)OtBu$, $-CO_2Et$, $-(CH_2)_2OH$, $-(CH_2)_2SMe$, $-CH_2CO_2tBu$, $-CH_2CO_2iBu$, $-(CH_2)_3OH$, $-(CH_2)_3NHCO_2tBu$, $-(CH_2)_2CO_2tBu$, $-(CH_2)_4OH$, $-(CH_2)_4NHCO_2tBu$, $-(CH_2)_5NH_2$, $-CH_2Ph$, $-CH_2$(4-OtBu)Ph, $-CH_2$(4-NH_2)Ph, $-CH_2$(4-NHCOMe)Ph, $-CH_2$(4-$NHCOCF_3$)Ph, $-CH_2$(4-SO_2Me)Ph, $-(CH_2)_2OH$, $-CH_2OH$, $-CH(CH_3)OH$, $-(CH_2)_3NH_2$, $-(CH_2)_4NH_2$, $-(CH_2)_2CO_2H$, $-CH_2$(4-OH)Ph, $-CH_2$(4-imidazolyl), $-CH_2CO_2H$, $-CONHCH_2CO_2Me$, $-CONH(CH_2)_2OMe$, -CONHiPr, -CO[1-(4-CO_2tBu)piperidinyl], -CO(4-morpholinyl), $-CONMe_2$, -CONHMe, $-CH_2CONHCH_2Ph$, $-CH_2CO$(4-morpholinyl), $-CH_2CO$(1-piperidinyl), $-CH_2CONH$(cyclopentyl), $-CH_2CO$[1-(2(S)-CO_2tBu)pyrrolidinyl], $-CH_2CONHMe$, $-CH_2CONHEt$, $-CH_2CONMe_2$, $-CH_2CONH(CH_2)_2OH$, $-CH_2CONH_2$, $-CH_2CONH(CH_2)_2CO_2tBu$, $-CH_2CONHCH_2CO_2tBu$, $-(CH_2)_2CO$(4-morpholinyl), $-(CH_2)_2CON[(CH_2)_2OH]_2$, $-(CH_2)_2CONH(CH_2)_5CO_2Me$, $-(CH_2)_2CONH(CH_2)_2OMe$, $-(CH_2)_2CONH(CH_2)_2O(CH_2)_2OH$, $-(CH_2)_2CON(iBu)_2$, $-(CH_2)_2CONHCH_2CO_2tBu$, $-(CH_2)_2CONH_2$, $-(CH_2)_2CONHMe$, $-(CH_2)_2CONMe_2$, $-(CH_2)_2CONHCH_2CONH_2$, $-CH_2OCH_2CO_2Me$, $-CH_2OEt$, $-CH_2OCH_2CONH_2$, $-(CH_2)_4NHCH_2Ph$, $-(CH_2)_4N(CH_2Ph)_2$, $-(CH_2)_4NMe_2$, $-(CH_2)_4OCOMe$, $-(CH_2)_4NHCOMe$, $-CH_2OCOMe$, $-(CH_2)_4NHSO_2Me$, $-CH_2$(4-$NHSO_2$Me)Ph, $-(CH_2)_3$[1-(4-$CONH_2$)piperidinyl], $-(CH_2)_3$[1-(4-CO_2tBu)piperidinyl], $-(CH_2)_3N(Me)CH_2CO_2tBu$, $-(CH_2)_4$(1-piperidinyl), (trans)-$CH_2CH=CHCO_2tBu$, $-(CH_2)_5CO_2Et$, $-CH_2CONH$(4-CO_2H)Ph, $-CH_2CONH(CH_2)_2CO_2H$, $-CH_2CONHCH_2CO_2H$, -CO[1-(4-CO_2H)piperidinyl], $-(CH_2)_2CONHCH_2CO_2H$, $-(CH_2)_3N(Me)CH_2CO_2H$, $-(CH_2)_3$[1-(4-CO_2H)piperidinyl], $-CH_2CO$[1-(2(S)-CO_2H)pyrrolidinyl], $-(CH_2)_5CO_2H$, $-(CH_2)_2S(O)Me$, $-(CH_2)_4NHCO_2Me$, $-CH_2OCONHPh$, $-(CH_2)_4NHCONHMe$, $-(CH_2)_4NH$(2-benzoxazolyl), $-CH_2OCH_2$(1-tetrazolyl), and $-(CH_2)_2NH_2$;

$R^{4''}$ is hydrogen;
$R^{5''}$ is hydrogen;
$R^{6''}$ is phenyl substituted with chloro;
$R^{7''}$ is unsubstituted or substituted C_{1-6}alkyl, hydrogen, or unsubstituted or substituted aryl;
$R^{8''}$ is unsubstituted or substituted C_{1-6}alkyl, hydrogen, or unsubstituted or substituted aryl, or;
$R^{7''}$ and $R^{8''}$ together represent a group $-(CH_2)_b$-Z-$(CH_2)_c$-;
b is 0 or 2 and c is 2 or 3, provided that when b is 0 then Z is unsubstituted or substituted methylene, and;
X and Y are as defined for formula (I) herein;
and salts and solvates thereof.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, pamoates, methanesulphonates, formates or trifluoroacetates.

Examples of solvates include hydrates.

Certain of the compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the stereoisomers of the compounds of formula (I), including geometric isomers and optical isomers, whether as individual stereoisomers or as mixtures thereof including racemic modifications.

Generally it is preferred that a compound of formula (I) is in the form of a single enantiomer or diastereoisomer.

Suitably, R^3 is derived from a corresponding D-amino acid.

Certain of the compounds of formula (I) may exist in one of several tautomeric forms. It will be understood that the present invention encompasses all of the tautomers of the compounds of formula (I) whether as individual tautomers or as mixtures thereof.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings, for example phenyl, and bicyclic carbocyclic aromatic rings, for example naphthyl.

References to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-4 heteroatoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include pyrimidinyl, imidazolyl, triazinyl, and tetrazolyl. Examples of bicyclic heterocyclic

aromatic rings include benzoxazolyl, thienopyrimidinyl, pyrazolopyrimidinyl, benzimidazolyl, and quinoxolinyl.

Suitable substituents for any aryl or heteroaryl group include alkyl, halo, nitro, amino, alkoxy, alkylcarbonylamino, perhaloalkylcarbonylamino, alkylsulphonyl, hydroxy, alkoxycarbonyl, alkylsulphonylamino, aminocarbonyl, and carboxy.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl, suitably containing up to six carbon atoms. It will be appreciated that references to alkenyl and alkylene shall be interpreted similarly.

Suitable substituents for any alkyl, alkenyl, or cycloalkyl group include alkoxy, hydroxy, alkylthio, alkoxycarbonyl, alkoxycarbonylamino, amino, aryl, carboxy, aralkylaminocarbonyl, heteroaryl, cycloalkylaminocarbonyl, heterocyclylcarbonyl, mono- and di-alkylaminocarbonyl, mono- and di-(hydroxyalkyl)aminocarbonyl, aminocarbonyl, alkoxycarbonylalkylaminocarbonyl, alkoxyalkylaminocarbonyl, hydroxyalkoxyalkylaminocarbonyl, aminocarbonylalkylaminocarbonyl, alkoxycarbonylalkoxy, aminocarbonylalkoxy, mono- or di-aralkylamino, mono-or di-alkylamino, alkylcarbonyloxy, alkylcarbonylamino, alkylsulphonylamino, heterocyclyl, alkoxycarbonylalkyl(alkyl)amino, carboxyalkylaminocarbonyl, carboxyalkyl(alkyl)amino, alkylsulphinyl, arylaminocarbonyloxy, alkylaminocarbonylamino, arylaminocarbonyl, heteroarylamino, and heteroarylalkoxy.

Examples of group J include pyrrolidinyl, piperidinyl, and morpholinyl.

References to C_{3-8} cycloalkyl include references to alicyclic isomers thereof i.e. moieties consisting of cycloalkyl groups substituted by alkyl groups, which moieties contain 3-8 carbon atoms.

References to "halogen" or "halo" include iodo, bromo, chloro or fluoro, especially fluoro and chloro.

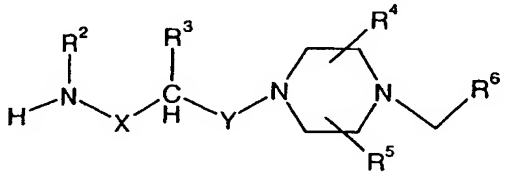
References to "heterocyclyl" include non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur. Each ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. Examples of heterocyclyl include piperidinyl, morpholinyl, and pyrrolidinyl.

Suitable substituents for any heterocyclyl group include aminocarbonyl, alkoxycarbonyl, and carboxy.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

There are provided Processes (a) to (g) according to the invention for preparing a compound of formula (I) which processes comprise:

Process (a): Reacting a compound of formula (II)



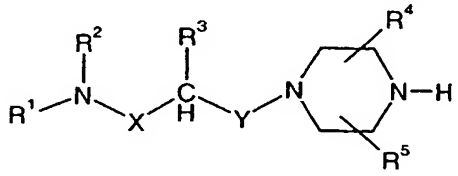
(II)

wherein;

R^2, R^3, R^4, R^5, R^6, X and Y are as defined in formula (I) above,

with a compound of formula R^1-L^1, wherein R^1 is as defined in formula (I) above, and L^1 represents a leaving group, suitably a halogen atom, such as chlorine, and optionally removing any necessary protecting group.

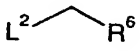
Process (b): Reacting a compound of formula (III)



(III)

wherein;

R^1, R^2, R^3, R^4, R^5, X and Y are as defined above, with a compound of formula (IV)

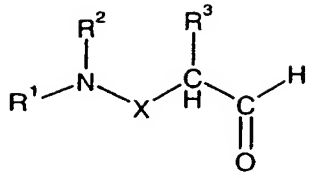


(IV)

wherein;

R^6 is as defined above and L^2 represents a leaving group, suitably a halogen atom, such as bromine, and optionally removing any necessary protecting group.

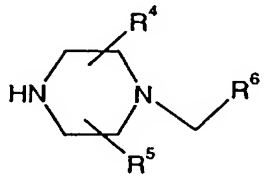
Process (c): Preparing a compound of formula (I) in which Y represents $-CH_2-$ by reacting a compound of formula (V)



(V)

wherein;

R^1, R^2, R^3 and X are as defined in formula (I), with a compound of formula (VI)

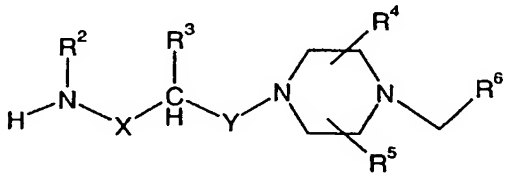


(VI)

wherein;

R^4, R^5 and R^6 are as defined in formula (I), followed by reduction of the resultant intermediate *in situ*, and optionally removing any necessary protecting group.

Process (d): Preparing a compound of formula (I) in which R^1 represents either unsubstituted or substituted 1,3-benzoxazol-2-yl by reacting a compound of formula (II)

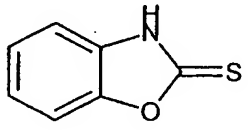


(II)

wherein;

R^2, R^3, R^4, R^5, R^6, X and Y are as defined in formula (I) above,

with a compound of formula (VII)

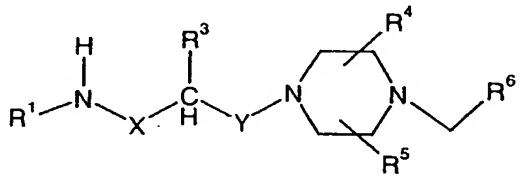


(VII)

wherein;

compounds of formula (VII) may be either unsubstituted or substituted with one or more substituents suitable for R^1, and optionally removing any necessary protecting group.

Process (e): Preparing a compound of formula (I) in which R^2 is other than hydrogen by reacting a compound of formula (I) in which R^2 represents hydrogen i.e. a compound of formula (Ia)



(Ia)

wherein;

R^1, R^3, R^4, R^5, R^6, X and Y are as defined in formula (I) above, with a compound of formula R^{2a}-L^3, wherein R^{2a} is C_{1-6} alkyl or C_{3-8} cycloalkyl, and L^3 represents a leaving group, suitably a halogen atom such as iodine, and optionally removing any necessary protecting group.

Process (f): Preparing a compound of formula (I) from another compound of formula (I), and optionally removing any necessary protecting group.

Process (a) may be performed in the presence of a suitable base eg. diisopropylethylamine under suitable conditions, eg. heating under reflux in a suitable solvent, eg. isopropanol.

Process (b) may be performed in the presence of a suitable base, eg. diisopropylethylamine in a suitable solvent eg. dichloromethane under suitable conditions, eg. ambient temperature.

Process (c) may be performed in the presence of a suitable solvent, eg. dichloromethane containing glacial acetic acid followed by the addition of a suitable reducing agent, eg. sodium triacetoxyborohydride.

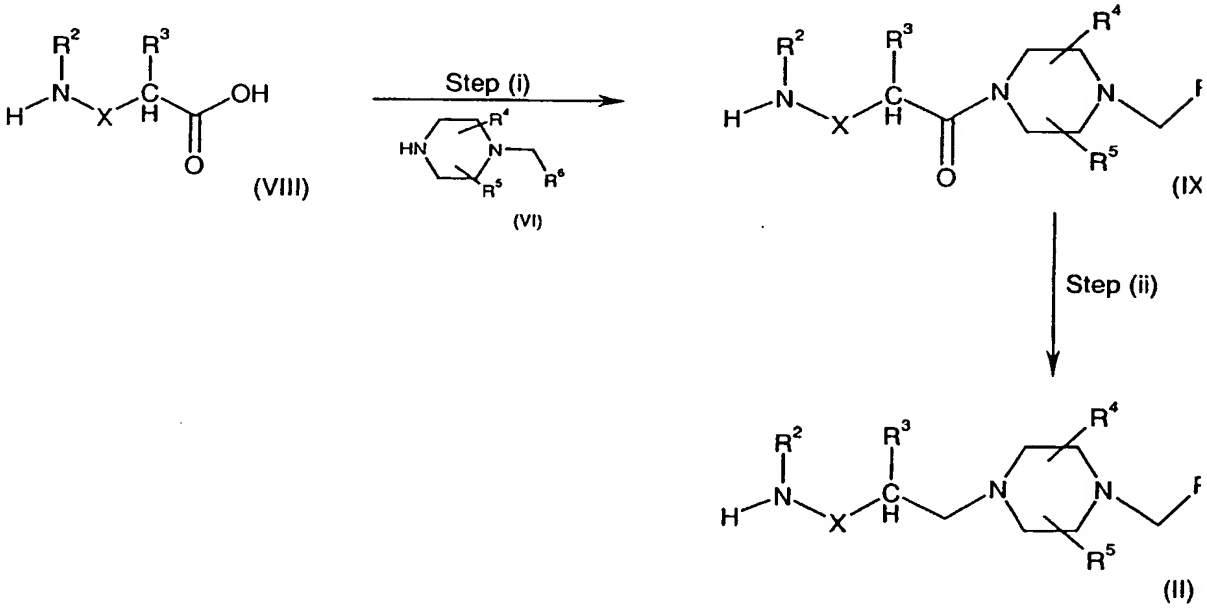
Process (d) may be performed in the presence of a suitable solvent eg. xylene under suitable conditions, eg. heating at 140ºC.

Process (e) may be performed in the presence of a suitable solvent eg. dimethylformamide and suitable reagents eg. sodium hydride and an alkyl halide, eg. methyl iodide at a suitable temperature, eg. ambient temperature.

Process (f) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, reductive alkylation, "Wittig" olefin synthesis, acylation, sulphonylation, esterification, urea formation, hydrolysis or aromatic substitution.

Examples of protecting groups and the means for their removal can be found in *T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991)*. Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis, or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid. Suitable hydroxyl and carboxylate protecting groups include alkyl (e.g. methyl or t-butyl), acetal (e.g. acetonide) and acyl (e.g. acetyl or benzoyl) which may be removed by hydrolysis, and arylalkyl (e.g. benzyl) which may be removed by catalytic hydrogenolysis.

Compounds of formula (II) in which Y represents -CH_2- may be prepared by a process comprising reaction of a compound of formula (VIII) or a protected derivative thereof, wherein R^2, R^3, R^4, R^5, R^6 and X are as defined in formula (I) above, with a compound of formula (VI) followed by reduction of the resultant product (see Scheme 1):



(VIII) (VI) (IX) (II)

Scheme 1

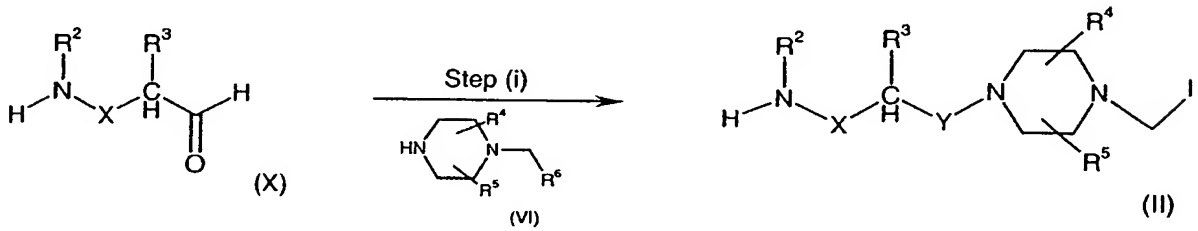
Step (i) comprises the use of suitable reagents for amide formation, eg. O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), dimethylformamide and diisopropylethylamine at a suitable temperature, eg. at ambient temperature. The free amine group of formula (VIII) is preferably protected eg. by 9-fluorenylmethoxycarbonyl (fmoc) or t-butoxycarbonyl (boc). Step (ii) comprises the use of suitable reducing agents, eg. borane-tetrahydrofuran complex, at a suitable temperature, eg. 65ºC.

Where compounds of formula (VIII) are protected, one step of the process of Scheme 1 will typically incorporate a deprotection reaction, as hereinbefore described.

In the course of the process of Scheme 1, it should be understood that deprotection or interconversion of other functional groups within the molecule may occur, either at step (i) or at step (ii).

The process described in Scheme 1 may be readily adapted for preparation of compounds of formula (II) in which Y represents $-(CH_2)_2-$.

Compounds of formula (II) may also be prepared according to the process shown in Scheme 2:



(X) (VI) (II)

Scheme 2

wherein;

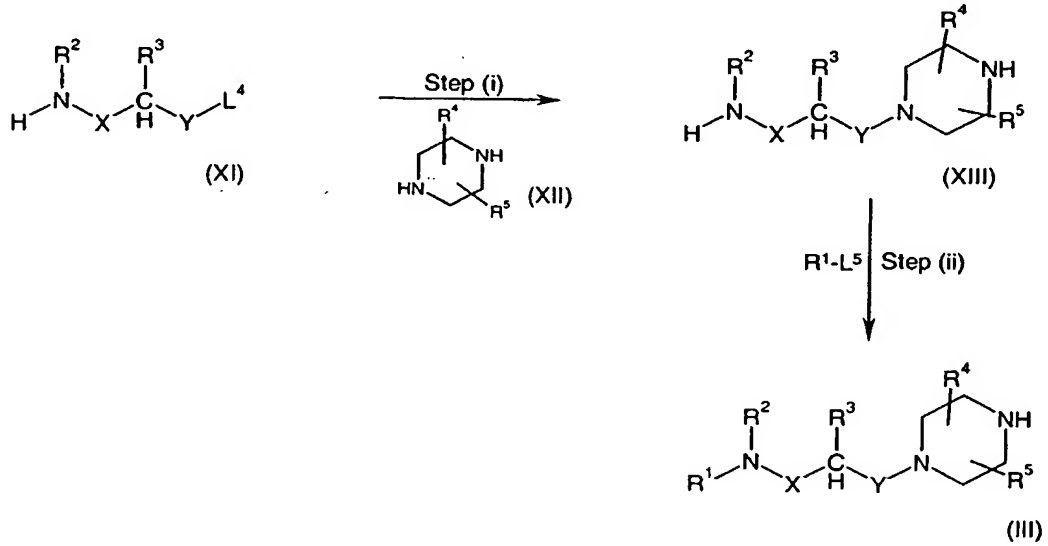
R^2, R^3, R^4, R^5, R^6, X and Y are as defined in formula (I) above.

Step (i) typically comprises reaction in the presence of a suitable reducing agent, eg. sodium triacetoxyborohydride, in a suitable solvent, eg. dichloromethane, containing glacial acetic acid. The free amine group of formula (X) is preferably protected eg. by 9-fluorenylmethoxycarbonyl (fmoc) or t-butoxycarbonyl (boc).

Where compounds of formula (X) are protected, completion of step (i) will typically comprise a deprotection reaction, as hereinbefore described.

In the course of the process of Scheme 2, it should be understood that deprotection or interconversion of other functional groups within the molecule may occur.

Compounds of formula (III) may be prepared by a process comprising reaction of a compound of formula (XI) or a protected derivative thereof according to the process of Scheme 3:



Scheme 3

wherein;

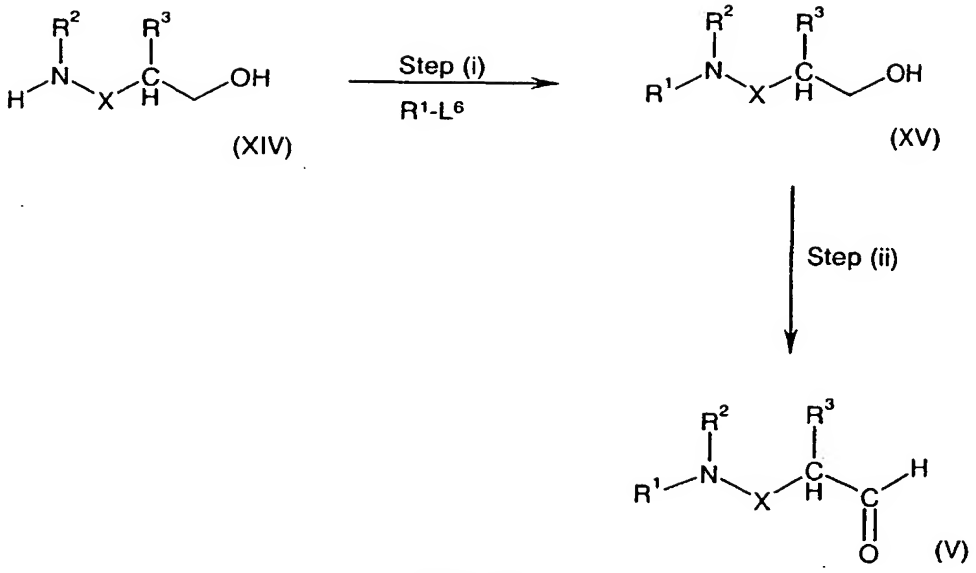
R^1, R^2, R^3, R^4, R^5, X and Y are as defined above, L^4 represents a leaving group, suitably a methanesulphonyloxy group or a halogen atom such as bromine, and L^5 represents a leaving group, suitably a halogen atom such as chlorine.

Step (i) typically comprises the use of a suitable solvent, eg. tetrahydrofuran and a suitable base, eg. diisopropyl ethylamine, under suitable reaction conditions, eg. heating under reflux. The free amine group of formula (X) is preferably protected eg. by t-butoxycarbonyl. Where compounds of formula (X) are protected, completion of step (i) will typically comprise a deprotection reaction, as hereinbefore described.

Step (ii) may typically be performed in the presence of a suitable base eg. diisopropylethylamine in suitable conditions, eg. heating under reflux in a suitable solvent eg. *iso*-propyl alcohol.

In the course of the process of Scheme 3, it should be understood that deprotection or interconversion of other functional groups within the molecule (e.g. the substituent R^3) may occur.

Compounds of formula (V) may be prepared according to the process of Scheme 4:



Scheme 4

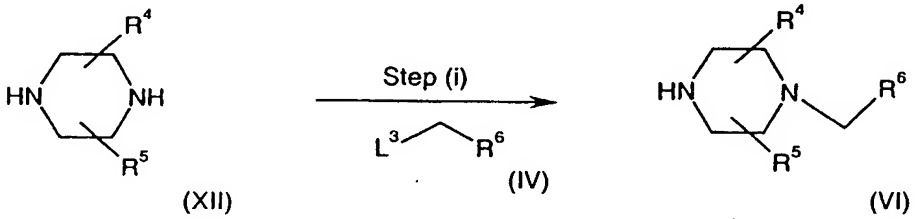
wherein;

R^1, R^2, R^3 and X are as defined in formula (I) above, and L^6 represents a leaving group, suitably a halogen atom such as chlorine.

Step (i) typically comprises the use of a suitable solvent, eg. isopropanol, and a suitable base, eg. diisopropylethylamine, under suitable conditions, eg. heating at reflux.

Step (ii) typically comprises a Swern oxidation reaction (K. Omura and D. Swern Tetrahedron **34**, 1651-1660, (1978)) in the presence of a suitable oxidising agent eg. the adduct formed from oxalyl chloride and dimethylsulphoxide, and a suitable solvent, eg. dichloromethane, and a suitable base, eg. diisopropylethylamine, at a reduced temperature (eg. –50ºC).

Compounds of formula (VI) or protected derivatives may be prepared according to the process of Scheme 5:



Scheme 5

wherein;

R^4, R^5 and R^6 are as defined in formula (I) above and L^3 represents a leaving group, suitably a halogen atom such as chlorine.

Step (i) typically comprises the use of a suitable base, eg. sodium bicarbonate in the presence of a suitable solvent, eg. ethanol, under suitable conditions, eg. heating at reflux. One of the free amine groups on compounds of formula (XI) may be protected eg. by a suitable amine protecting group as described above.

Compounds of formulae (IV), (VII), (VIII), (XI), (XII) and (XIV) are either known or may be prepared in accordance with known procedures, for example those disclosed in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

Compounds of formulae (II) and (III) in protected and unprotected forms are believed to be new and also form an aspect of the invention.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(a) CCR-3 Binding Assay

A CCR-3 competition binding SPA (scintillation proximity assay) was used to assess the affinity of novel compounds for CCR-3. Membranes prepared from K562 cells stably expressing CCR-3 (2.5µg/well) were mixed with 0.25mg/well wheat-germ agglutinin SPA beads (Amersham) and incubated in binding buffer (HEPES 50 mM, $CaCl_2$ 1 mM, $MgCl_2$ 5 mM, 0.5% BSA) at 4°C for 1.5 hr. Following incubation, 20 pM of [^{125}I] eotaxin (Amersham) and increasing concentrations of compound (1pM to 30µM) were added and incubated in a 96 well plate for 2 hr at 22°C then counted on a Microbeta plate counter. The total assay volume was 100 µl. Competition binding data were analysed by fitting the data with a four parameter logistic equation. Data are presented as the mean pIC_{50} values (negative logarithm of the concentration of compound which inhibits [^{125}I]eotaxin binding by 50%) from at least two experiments.

(b) Eosinophil Chemotaxis Assay.

Compounds were evaluated for their inhibitory effect on eosinophil chemotaxis. Eosinophils were purified from human peripheral blood by standard CD16 cell depletion using a Miltenyi cell separation column and a magnetic Super Macs magnet as previously described (Motegi & Kita, 1998; J.Immunology. 161:4340-6). Cells were re-suspended in RPMI 1640/10% FCS solution and incubated with calcein-AM (Molecular Probes) at 37°C for 30 mins. Following incubation, the eosinophils were centrifuged at 400g for 5 min and re-suspended in RPMI/FCS at 2.2 million/ml. Cells were then incubated in the

presence of increasing concentration of compounds (1 pM to 30 μM) at 37°C for 30 mins. For control responses cells were incubated with RPMI/FCS only. The agonist eotaxin (an EC_{80} concentration) was added to the lower chamber of a 96 well chemotaxis plate (5 μm filter: Receptor Technologies). Eosinophils (50 μl of 2 million/ml cells) were added to the top chamber of the filter plate and incubated at 37°C for 45 mins. Cells remaining on top of the chemotaxis filter were removed and the number of eosinophils which had migrated were quantified by reading the plate on a fluorescent plate reader. Inhibition curves for the effect of compounds on eosinophil chemotaxis were analysed by fitting the data with a four parameter logistic equation. Functional pK_i values (fpK_i) were generated using the equation below (Lazareno & Birdsall, 1995. Br.J.Pharmacol 109: 1110-9).

$$fpKi = \frac{IC_{50}}{1 + \frac{[Agonist]}{EC_{50}}}$$

Results

The compounds of the Examples were tested in the CCR-3 binding and/or eosinophil chemotaxis assays (assays (a) and (b) respectively). The compounds of the Examples tested in the CCR-3 binding assay possessed pIC_{50} values in the range 5-8. The compounds of the Examples tested in the CCR-3 eosinophil chemotaxis assay possessed fpKi values in the range 5.5-7.5.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as bronchitis (including chronic bronchitis), asthma (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD) and rhinitis.

Also included are diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure.

Furthermore, compounds of the invention may be used to treat nephritis; skin diseases such as psoriasis, eczema, allergic dermatitis and hypersensitivity reactions; and diseases of the central nervous system which have an inflammatory component (eg. Alzheimer's disease, meningitis, multiple sclerosis), HIV and AIDS dementia.

Compounds of the present invention may also be of use in the treatment of nasal polyposis, conjunctivitis or pruritis.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiovascular conditions such as atherosclerosis, peripheral vascular disease and idiopathic hypereosinophilic syndrome.

Compounds of the invention may be useful as immunosuppressive agents and so have use in the treatment of auto-immune diseases such as allograft tissue rejection after transplantation, rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

Diseases of principal interest include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful as therapeutic agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

There is also therefore provided a compound of formula (I), or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, eg. asthma or rhinitis.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with inflammatory conditions, eg. asthma or rhinitis.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition eg. asthma or rhinitis, which method comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way.

There is thus further provided a pharmaceutical composition comprising a compound of formula (I), or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

There is also provided a process for preparing such a pharmaceutical formulation which comprises admixing the compound of formula (I) or a physiologically acceptable salt or solvate thereof with one or more physiologically acceptable diluents or carriers.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, parenteral or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multidose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

The compounds and pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example antihistaminic agents, anticholinergic agents, anti-inflammatory agents such as corticosteroids, e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide; or non-steroidal anti-inflammatory drugs (NSAIDs) eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists; or beta adrenergic agents such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof; or antiinfective agents e.g. antibiotic agents and antiviral agents. It will be appreciated that when the compounds of the present invention are administered in combination with other therapeutic agents normally administered by the inhaled or intranasal route, that the resultant pharmaceutical composition may be administered by the inhaled or intranasal route.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.001 to 500mg/kg body weight, preferably 0.01 to 500mg/kg body weight, more preferably 0.01 to 100mg/kg body weight, and at any appropriate frequency e.g. 1 to 4 times daily. The precise dosing regimen will of course depend on factors such as the therapeutic indication, the age and condition of the patient, and the particular route of administration chosen.

It should be noted that throughout the description and the claims, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The invention is illustrated by reference to, but is in no way limited by, the following Examples.

It should be noted that, for clarity, compounds of the Descriptions and the Examples are referred to by number, for example "Description 3" and "Example 26". The structures of the compounds so referred to are given in Tables 1 to 4 for the Examples and Tables 5 to 9 for the Descriptions.

General Experimental Details

Standard Automated Preparative HPLC column, conditions and eluent

Automated preparative high performance liquid chromatography (autoprep. HPLC) was carried out using a Supelco+ 5µm (100mm x 22mm internal diameter) column eluted with a mixture of solvents consisting of (i) 0.1%

trifluoroacetic acid in water and (ii) 0.1% trifluoroacetic acid in acetonitrile, the eluent being expressed as the percentage of (ii) in the solvent mixture, at a flow rate of 4ml per minute.

Liquid Chromatography Mass Spectrometry (LC/MS) System
The following (LC/MS) system was used:

System A
This system used a 3µm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents: (A) – 0.1% v/v formic acid + 0.077% w/v ammonium acetate in water; and (B) – 95:5 acetonitrile:water + 0.05% v/v formic acid, at a flow rate of 3 ml per minute. The following gradient protocol was used: 100% (A) for 0.7mins; (A)+(B) mixtures, gradient profile 0 – 100% (B) over 3.5mins; hold at 100% (B) for 1.1mins; return to 100% (A) over 0.2mins.

Synthetic Method A
Example 1
A solution of 4-[(3,4-dichlorophenyl)methyl]-α-(1-methylethyl)-1-piperazineethanamine [CAS 220772-45-2] (0.536g) in propan-2-ol (20ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.37ml) and diisopropylethylamine (0.28ml) and the resulting solution was heated under reflux for 18h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 20g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.51g), from ethyl acetate/cyclohexane (1:1), as an orange gum.
LC-MS (System A): Rt = 3.09min. Mass Spectrum *m/z* 447[MH^+]

Synthetic Method B
Example 12
A solution of the compound of Description 3 (0.061g) in propan-2-ol (5ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.04ml) and diisopropylethylamine (0.06ml) and the resulting solution was heated under reflux for 18h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.07g) from ethyl acetate/cyclohexane (1:1), as a pale amber gum.
LC-MS (System A): Rt = 3.11min. Mass Spectrum *m/z* 461[MH^+]

The starting material for Example 12 may be prepared according to Descriptions 1-3 below.

Description 1

A mixture of fmoc D-leu-OH [CAS 114360-54-2] (0.34g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU", 2ml from a 0.5M stock solution) in anhydrous dimethylformamide (5ml) was left standing at room temperature for 15min. The resulting solution was then treated with 4ml from a stock solution containing 0.5M 1-[(3,4-dichlorophenyl)methyl]piperazine [CAS 55513-17-2] and 1.0M diisopropylethylamine in dimethylformamide. The resulting mixture was left standing at room temperature overnight. The solvent was removed by vacuum centrifugation. Chromatographic purification of the crude product mixture on silica (Varian Bond- Elut™,10g), eluting with a gradient of ethyl acetate/cyclohexane, gave the title compound (0.56g) as a white foam.
LC-MS (System A): Rt = 4.03min.

Description 2

A solution of the compound of Description 1 (0.46g) in tetrahydrofuran (5ml) was treated with a 1.0M solution of Borane/THF complex in THF (8ml) and the resulting mixture was heated at 65°C for 18h. The cooled mixture was quenched with methanol and stirred for 24h then concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 10g), eluting with a gradient of ethyl acetate/cyclohexane, gave the title compound (0.28g) from 1:1 ethyl acetate:cyclohexane as a colourless gum.
LC-MS (System A): Rt = 3.42min.

Description 3

The compound of Description 2 (0.28g) was treated with a 20% solution of piperidine in tetrahydofuran (10ml) and the resulting mixture was left to stand at room temperature for 1 hour. The solution was concentrated *in vacuo*. Chromatographic purification of the residue on silica (Varian Bond-Elut™, 5g) gave the title compound (0.125g), from ethyl acetate/methanol (1:1), as a white solid.
LC-MS (System A): Rt = 2.14min.

Synthetic Method C

Example 26

A solution of the compound of Description 7 (0.070g) in propan-2-ol (5ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.035ml) and diisopropylethylamine (0.052ml) and the resulting solution was heated under reflux for 18h. The solution was concentrated *in vacuo*. Chromatographic

purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate and then ethyl acetate/methanol, gave the title compound (0.07g), from ethyl acetate and ethyl acetate/methanol (19:1), as a pale amber gum.
LC-MS (System A): Rt = 3.20min. Mass Spectrum *m/z* 576[MH^+]

The starting material for Example 26 may be prepared according to Descriptions 4-7 below.

Description 4
A solution of fmoc-D-lys(boc)-OH [CAS 92122-45-7] (0.76g) in anhydrous THF(20ml) was treated with N,O-dimethylhydroxylamine hydrochloride (0.12g), 1-hydroxybenzotriazole hydrate (0.24g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride [CAS 25952-53-8] (0.37g) and diisopropylethylamine (0.94ml) and the resulting solution was stirred at room temperature for 18h. The mixture was diluted with diethyl ether (50ml), washed with saturated sodium bicarbonate (30ml) and brine (30ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (0.82g) as a clear oil.
LC-MS (System A): Rt = 3.74min.

Description 5
A solution of the compound of Description 4 (0.82g) in anhydrous THF (10ml) was cooled to -78°C, under nitrogen, and a 1.0M solution of lithium aluminium hydride in diethyl ether (0.72ml) was added dropwise. The mixture was stirred at -78°C for 1h then quenched by the dropwise addition of a saturated solution of ammonium chloride (10ml). Diethyl ether (20ml) was added to the mixture and the biphasic mixture was vigorously stirred at room temperature for 1h. The resulting suspension was further diluted with diethyl ether (20ml). The organic phase was separated, washed sequentially with saturated sodium bicarbonate solution (20ml) and brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (0.72g) as a colourless gum.
LC-MS (System A): Rt = 3.47min.

Description 6
The compound of Description 5 (0.72g) was dissolved in dichloromethane (15ml) and the resulting solution was treated with 1-[(3,4-dichlorophenyl)methyl]piperazine [CAS 55513-17-2] (0.39g), sodium triacetoxyborohydride (0.68g) and glacial acetic acid (0.23ml). The resulting suspension was stirred at room temperature for 2 days. The mixture was diluted with dichloromethane (30ml) and washed with saturated sodium bicarbonate

solution (2x20ml). The aqueous layer was extracted with dichloromethane (20ml) and the combined organics were washed with brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (40g Biotage), eluting with cyclohexane/ethyl acetate gradient, gave the title compound (0.11g) from ethyl acetate as a white foam.
LC-MS (System A): Rt = 3.65min.

Description 7
The compound of Description 6 (0.10g) was treated with a 20% solution of piperidine in THF (5ml) and the resulting mixture was left standing at room temperature for 1 hour. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g) gave the title compound (0.07g) from methanol as a white solid.
LC-MS (System A): Rt = 2.56 min.

Synthetic Method D
Example 17
A solution of the compound of Description 10 (0.060g) in 1.0ml of a (1:1) mixture of trifluoroacetic acid and dichloromethane (1ml) was left to stand for 0.5h then concentrated *in vacuo*. The residue was partitioned between dichloromethane (5ml) and 1.0M sodium bicarbonate (5ml). The organic phase was separated and concentrated to give a yellow gum (0.031g). A mixture of this gum (0.031g), 2-chlorobenzoxazole [CAS 615-18-9] (0.03ml) and diisopropylethylamine (0.06ml) in propan-2-ol was heated at 75°C overnight, cooled and concentrated *in vacuo*.. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.014g) from ethyl acetate as a pale yellow oil.
LC-MS (System A): Rt = 2.81min. Mass Spectrum *m/z* 477[MH^+].

The starting material for Example 17 may be prepared according to Descriptions 8-10 below.

Description 8
A solution of potassium hydroxide (1.12g) in ethanol (25ml) was added dropwise at 0°C to a solution of diethyl [(tert-butoxycarbonyl)amino]malonate [CAS 102831-44-7] (5.5g) in ethanol (25ml). The mixture was stirred at room temperature for 1.5h then concentrated *in vacuo*. The residue was partitioned between water and diethyl ether. The aqueous phase was acidified with dilute hydrochloric acid to pH5 and extracted with ethyl acetate. The aqueous layer

was evaporated and combined with the residue obtained by concentration of the ethyl acetate extracts to give the title compound (3.6g) as a colourless gum.
LC-MS (System A): Rt = 2.41min.

Description 9

A solution of the compound of Description 8 (3.5g) in dry tetrahydrofuran (60ml) was treated with N,O-dimethylhydroxylamine hydrochloride (1.66g), 1-hydroxy-7-azabenzotriazole (2.1g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride [CAS 25952-53-8] (3.3g) and diisopropylethylamine (5.4ml) and the resulting white suspension was stirred for 3 days. The mixture was diluted with diethyl ether (100ml), washed with saturated sodium bicarbonate (100ml) and brine (100ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 50g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (3.68g) from 1:1 ethyl acetate:cyclohexane as a colourless, viscous oil.
LC-MS (System A): Rt = 2.68min.

Description 10

A solution of the compound of Description 9 (3.68g) in dry tetrahydrofuran was treated with a 1.0M solution of lithium tri-tert-butoxy aluminohydride in tetrahydrofuran (25.4ml) and the clear solution was stirred at room temperature for 2 hours. After cooling, the mixture was quenched by dropwise addition of a 5% solution of potassium hydrogen sulphate (75ml).The resultant suspension was stirred at room temperature for 1.5h. The mixture was extracted with diethyl ether (2x100ml) and the combined organic extracts were washed with a saturated solution of sodium bicarbonate (100ml) and brine (100ml) then dried ($MgSO_4$) and concentrated *in vacuo* to give the intermediate aldehyde (2.8g) as a colourless oil. A solution of this oil in dry dichloromethane (100ml) was treated with sodium triacetoxyborohydride (5.38g), acetic acid (1.82ml) and 1-[(3,4-dichlorophenyl)methyl]piperazine [CAS55513-17-2] (3.42g) and the mixture was stirred at room temperature overnight. The mixture was washed with a saturated solution of sodium bicarbonate (2x50ml) and brine (2x500ml) then dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 50g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (1.66g) from 1:1 ethyl acetate:cyclohexane as a colourless gum.
LC-MS (System A): Rt = 2.68min.

Synthetic Method E

Example 18

A solution of the compound of Description 13 (0.5g) in propan-2-ol (15ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.34ml) and triethylamine (0.21ml) and the resulting solution was heated under reflux for 18h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 20g), eluting with a gradient of ethyl acetate/methanol, gave the title compound (0.33g) from 5% methanol/ethyl acetate, as a white solid.
LC-MS (System A): Rt = 2.65min. Mass Spectrum *m/z* 449[MH^+]

The starting material for Example 18 may be prepared according to Descriptions 11-13 below.

Description 11
A solution of fmoc-D-asp(OtBu)-OH [CAS 112883-39-3] (0.92g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU", 1.08g) in anhydrous dimethylformamide (20ml) was left standing at room temperature for 5min. 1-[(3,4-Dichlorophenyl)methyl]piperazine [CAS 55513-17-2] (0.77g) and diisopropylethylamine (0.846ml) were added. The resulting mixture was left standing at room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and 0.5M sodium bicarbonate, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond- Elut™, 50g), eluting with 1:1 ethyl acetate/cyclohexane, gave the title compound (1.4g) as a colourless gum.
LC-MS (System A): Rt = 3.86min.

Description 12
A solution of the compound of Description 11 (1.4g) in tetrahydrofuran containing 20% v/v piperidine (10ml) was left to stand for 30 minutes. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 20g), eluting with a gradient of ethyl acetate then 10% methanol/ethyl acetate, gave the title compound (0.67g) from 10% methanol/ethyl acetate as a colourless oil.
LC-MS (System A): Rt = 2.46min.

Description 13
A solution of the compound of Description 12 (0.6g) in tetrahydrofuran (10ml) was treated with a 1.0M solution of borane/THF complex in THF (15ml) and the resulting mixture was heated at reflux for 18h. The cooled mixture was quenched by addition of methanol (50ml). The resultant solution was stirred for 18h at room temperature then concentrated *in vacuo* to give the title compound (0.48g) as a colourless oil.

LC-MS (System A): Rt = 0.92min.

Synthetic Method F

Example 19

A solution of the compound of Description 16 (0.072g), 2-chlorobenzoxazole [CAS 102-47-6] (0.046g) and diisopropylethylamine (0.129g) in propan-2-ol (10ml) was heated at reflux for 18h. The solution was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (20ml) and 0.5M sodium bicarbonate (15ml). The organic phase was separated, washed with water (25ml), dried (Na_2SO_4) and evaporated to give a gum. Salt formation (1.0M hydrogen chloride in ether) gave the title compound (0.101g) as a white powder.
LC-MS (System A): Rt = 2.97min. Mass Spectrum *m/z* 479[MH^+]

The starting material for Example 19 may be prepared according to Descriptions 14 to 16 below.

Description 14

A solution of BOC-D-met-OH [CAS 5241-66-7] (0.274g) and O-(7-azabenzotriazol-1-yl)-N,N,N^1,N^1-tetramethyluronium hexafluorophosphate ("HATU", 0.420g) in acetonitrile (10ml) was stirred for 5 min. then treated with a solution of 1-[(3,4-dichlorophenyl)methyl]piperazine dihydrochloride [CAS 55513-17-2] (0.318g) and diisopropylethylamine (0.387g) in acetonitrile (10ml). The reaction mixture was stirred for 4h then left to stand overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (25ml) and 0.5M sodium bicarbonate (20ml). The organic phase was separated, washed consecutively with 2% w/v citric acid (25ml) and water (25ml), dried (Na_2SO_4) and evaporated to give the title compound (0.480g) as a colourless gum.
LC-MS (System A): Rt = 3.07min.

Description 15

A solution of 4.0M hydrogen chloride in dioxan (2ml) was added to a stirred solution of the compound of Description 14 (0.470g) in dichloromethane (10ml). The reaction mixture was stirred for 4h, left to stand overnight then concentrated *in vacuo*. The residue was washed with diethyl ether and dried *in vacuo* to give the title compound (0.440g) as a cream powder.
LC-MS (System A): Rt = 2.20min.

Description 16

A suspension of the compound of Description 15 (0.165g) in tetrahydrofuran (20ml) was treated with a 1.0M solution of borane/THF complex in THF (5ml) and the resulting mixture was heated at reflux for 5.5h then cooled to 20°C. More 1.0M Borane-THF complex (2.5ml) was added. The reaction mixture was heated at reflux for a further 5.5h, cooled to 20°C, treated with methanol (10ml) and concentrated *in vacuo.* to leave a gum. Chromatographic purification of the gum on silica (Varian Bond-Elut™, 20g), eluting with a mixture of dichloromethane, ethanol and ammonia [initially (100:8:1) and then (100:15:1) to elute the product] gave the title compound (0.221g) as a colourless gum.
LC-MS (System A): Rt = 2.01min.

Synthetic Method G

Example 21

A solution of the compound of Description 22 (0.3g) in propan-2-ol (5ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.17ml) and triethylamine (0.104ml) and the resulting solution was heated under reflux for 18h. The solution was concentrated *in vacuo.* Chromatographic purification on silica (Varian Bond-Elut™, 20g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.31g) from ethyl acetate/cyclohexane (1:2) as a colourless gum.
LC-MS (System A): Rt = 2.83min. Mass Spectrum *m/z* 519[MH^+]

The starting material for Example 21 may be made according to Descriptions 17-22 below.

Description 17

A solution of fmoc-D-asp(OtBu)-OH [CAS 112883-39-3] (5.0g) in anhydrous THF (50ml) was cooled to −10°C and treated with triethylamine (1.23g) and isobutyl chloroformate (1.99g). The reaction mixture was stirred for 1 hour. Sodium borohydride (0.92g) was added portionwise and the reaction mixture was stirred for 2 hours. The mixture was quenched by addition of water (25ml), diluted with water (200ml) and extracted with dichloromethane (200ml). The extracts were washed with 2M hydrochloric acid (50ml), 0.5M sodium bicarbonate (50ml) and brine (50ml), dried ($MgSO_4$) and concentrated *in vacuo.* Chromatographic purification on silica (90g Biotage), eluting with 3:2 cyclohexane/ethyl acetate, gave the title compound (4.34g) as a white solid.
LC-MS (System A): Rt = 3.30min.

Description 18

A stirred solution of oxalyl chloride (1.44g) in dichloromethane (10ml), under nitrogen at –60°C, was treated dropwise with dimethyl sulphoxide (1.61ml) in dichloromethane (5ml). The solution was stirred for 5 minutes. A solution of the compound of Description 17 (4.1g) in dichloromethane (20ml) was added and the mixture was stirred for 45 minutes. Triethylamine (3.16ml) was added and the reaction mixture was allowed to warm to 0°C. Water (50ml) was added. The organic phase was separated, washed with 2M hydrochloric acid, 0.5M sodium bicarbonate and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (4.0g) as colourless gum.
LC-MS (System A): Rt = 3.31min.

Description 19

A solution of the compound of Description 18 (4.0g) in dichloromethane (30ml) was treated with 1-[(3,4-dichlorophenyl)methyl]piperazine [CAS 55513-17-2] (3.5g), sodium triacetoxyborohydride (2.12g) and glacial acetic acid (1.42ml). The resulting suspension was stirred for 18 hours. The mixture was diluted with dichloromethane (30ml) and washed with saturated sodium bicarbonate solution (2x20ml). The combined aqueous phases were extracted with dichloromethane (20ml) and the combined organic extracts were washed with brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond- Elut™, 70g), eluting with cyclohexane/ethyl acetate gradient, gave the title compound (5.3g) from ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 3.35min.

Description 20

A solution of the compound of Description 19 (1.27g) in dichloromethane (10ml) was treated with a (1:1) mixture of trifluoroacetic acid and dichloromethane (10ml). The reaction mixture was left to stand for 3 hours. The mixture was concentrated *in vacuo* to give the title compound (2.1g) as an orange glass.
LC-MS (System A): Rt = 3.12min.

Description 21

A solution of the compound of Description 20 (2.0g) in dry tetrahydrofuran (25ml) was cooled to –10°C and treated with isobutyl chloroformate (0.39ml) and triethylamine (1.05ml). The resulting solution was stirred for 1 hour. Sodium borohydride (0.191g) was added and the solution was stirred for 2 hours at 0°C. Water was added. The product mixture was partitioned between dichloromethane (50ml) and water (50ml). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification of the

residue on silica (Varian Bond- Elut™, 10g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.6g) from ethyl acetate/cyclohexane (1:1), as a colourless oil.
LC-MS (System A): Rt 3.38min.

Description 22
A solution of the compound of Description 21 (0.60g) in a mixture of piperidine (2ml) and tetrahydrofuran (8ml) was left to stand for 30 minutes. The solution was concentrated *in vacuo*. Chromatographic purification of the residue on silica (Varian Bond-Elut™, 10g), eluting with a gradient of ethyl acetate then 10% methanol/ethyl acetate, gave the title compound (0.31g) from 10% methanol/ethyl acetate as a colourless gum.
^{1}H NMR δ ($CDCl_3$) 7.4 (1H, d), 7.35 (1H, d), 7.15 (1H, d), 3.9 (2H, m), 3.4 (2H, s), 3.35 (1H, m), 2.7-2.3 (9H, broad), 2.3-2.2 (3H, m), 2.0-1.9 (1H, m), 1.8 (2H, broad), 0.9 (6H, d).

Synthetic Method H
Example 22
A mixture of the compound of Description 26 (0.248g), 2-chlorobenzoxazole [CAS 102-47-6] (0.100g) and diisopropylethylamine (0.160g) in propan-2-ol (15ml) was heated at reflux for 6h, cooled and concentrated *in vacuo* to leave a gum. Chromatographic purification of the gum on silica (Varian Bond-Elut™, 20g), eluting initially with ethyl acetate (to remove impurities) and then with a (100:8:1) mixture of dichloromethane, ethanol and ammonia, gave a gum. The gum was dissolved in ethyl acetate (25ml). The solution was washed with water (3x25ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.108g) as a colourless glass.
LC-MS (System A): Rt = 2.69min. Mass Spectrum *m/z* 463[MH^+]

The starting material for Example 22 may be prepared according to Descriptions 23-26 below.

Description 23
A solution of fmoc-D-glu(OtBu)-OH [CAS 104091-08-9] (0.425g) and O-(7-azabenzotriazol-1-yl)-N,N,N^1,N^1-tetramethyluronium hexafluorophosphate ("HATU", 0.405g) in acetonitrile (25ml) was stirred for 10min then treated with a solution of 1-[(3,4-dichlorophenyl)methyl]piperazine dihydrochloride [CAS 55513-17-2] (0.318g) and diisopropylethylamine (0.387g) in acetonitrile (10ml). The reaction mixture was stirred for 1.25h then left to stand for 3 days. The solvent was removed *in vacuo*. The residue was partitioned between ethyl

acetate (50ml) and 0.5M sodium bicarbonate (30ml). The organic phase was separated, washed with 0.25M sodium bicarbonate (30ml) and water (30ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.614g) as a cream foam.
LC-MS (System A): Rt = 3.91min.

Description 24
A solution of 4.0M hydrogen chloride in dioxan (2.5ml) was added to a stirred solution of the compound of Description 23 (0.600g) in dichloromethane (25ml). The reaction mixture was stirred for 2.5h. More 4.0M hydrogen chloride in dioxan (3ml) was added and stirring was continued for 16h. The reaction mixture was concentrated *in vacuo*. The residue was washed with diethyl ether and dried *in vacuo* to give the title compound (0.582g) as a yellow solid.
LC-MS (System A): Rt = 3.43min.

Description 25
A solution of the compound of Description 24 (0.360g) in piperidine (3ml) and tetrahydrofuran (12ml) was stirred for 2h. The reaction mixture was concentrated to leave a semi-solid, which was triturated in ethyl acetate (30ml) for 0.5h. The suspension was left to stand overnight. The solvent was decanted and the residue was dried *in vacuo* to give the crude title compound (0.283g) as a cream powder.
LC-MS (System A): Rt = 2.10min.

Description 26
A solution of the compound of Description 25 (0.270g) in tetrahydrofuran (35ml) and a 1.0M solution of Borane/THF complex in THF (7.5ml) was stirred and heated at reflux for 16h. The solution was cooled to 20°C and treated, with stirring, with methanol (10ml). The resultant solution was stirred for 0.5h then concentrated *in vacuo* to give the crude title compound (0.268g) as a pale yellow gum.
LC-MS (System A): Rt = 1.76min.

Synthetic Method J

Example 27
A mixture of the compound of Description 30 (0.140g), 2-chlorobenzoxazole [CAS 102-47-6] (0.039 g) and diisopropylethylamine (0.200g) in isopropanol (28ml) was stirred and heated at reflux for 6h. The cooled mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (25ml) and 0.25M sodium bicarbonate (20ml). The organic phase was separated,

washed with water (20ml), dried (Na_2SO_4) and concentrated *in vacuo*. . Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting initially with dichloromethane and then with a (100:8:1) mixture of dichloromethane, ethanol and ammonia, gave the title compound (0.020g), from a (100:8:1) mixture of dichloromethane, ethanol and ammonia, as a colourless gum.
LC-MS (System A): Rt = 2.50min. Mass Spectrum *m/z* 490[MH^+]

The starting material for Example 27 may be prepared according to Descriptions 27-30 below.

Description 27

A solution of (DL)-homolysine [CAS 498-56-6] (0.144g), di-tert-butyl dicarbonate (0.480g) and diisopropylethylamine (0.387g) in water (15ml) and tetrahydrofuran (15ml) was stirred for 6h then left to stand overnight. The solvents were removed *in vacuo*. The residue was partitioned between ethyl acetate (2x25ml) and 1% w/v citric acid (25ml). The combined organics were dried (Na_2SO_4) and concentrated to give the title compound (0.152g) as a colourless gum.
Tlc (Silica, ethyl acetate): Rf = 0.75. $KmnO_4$ detection.

Description 28

A mixture of the compound of Description 27 (0.144g) and O-(7-azabenzotriazol-1-yl)-N,N,N^1,N^1-tetramethyluronium hexafluorophosphate ("HATU", 0.170g) in acetonitrile (3ml) was stirred for 5 min then treated with a solution of 1-[(3,4-dichlorophenyl)methyl]piperazine dihydrochloride [CAS 55513-17-2] (0.140g) and diisopropylethylamine (0.129g) in acetonitrile (3ml). The reaction mixture was stirred for 2h then left for 3 days. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (30ml) and 0.5M sodium bicarbonate (20ml). The organic phase was separated, washed consecutively with water (20ml), 2% w/v citric acid (20ml) and water (20ml), dried (Na_2SO_4) and evaporated to give the title compound (0.237g) as a pale yellow foam.
LC-MS (System A): Rt = 3.35min.

Description 29

A solution of 1.0M hydrogen chloride in dioxan (2ml) was added to a stirred solution of the compound of Description 28 (0.228g) in dichloromethane (10ml). The solution (which later became a suspension) was stirred for 6h then concentrated *in vacuo*. The residue was washed with diethyl ether and dried *in vacuo* to give the title compound (0.182g) as a yellow powder.
LC-MS (System A): Rt = 1.72min.

Description 30

A suspension of the compound of Description 29 (0.165g) in tetrahydrofuran (20ml) was treated with a 1.0M solution of borane/THF complex in THF (4ml) and the resulting mixture was heated at reflux for 6.5h then cooled to 20°C. More 1.0M borane/THF complex (2.5ml) was added. The reaction mixture was heated at reflux for a further 3.5h, cooled to 20°C, treated with methanol (10ml) and concentrated *in vacuo*. A solution of the residue in a mixture of methanol (3ml) and ethyl acetate (25ml) was treated with 1.0M ethereal hydrogen chloride. The solvents were decanted from the resultant precipitate to leave the title compound (0.151g) as a yellow powder.
LC-MS (System A): Rt = 1.33min.

Synthetic Method K

Example 28

A solution of the compound of Description 34 (0.068g) in propan-2-ol (2ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.041ml) and triethylamine (0.025ml) and the resulting solution was heated under reflux for 2h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.073g) from ethyl acetate/cyclohexane (1:4), as a colourless gum.
LC-MS (System A): Rt = 3.25min. Mass Spectrum *m/z* 495[MH^+]

The starting material for Example 28 may be prepared according to Descriptions 31-34 below.

Description 31

A solution of D-phenylalanine [CAS 673-06-3] (6.58g) in (1:1) isopropanol/water (200ml) was treated with a mixture of di-*tert*-butyl dicarbonate (11.3g) and triethylamine (4.0g) in isopropanol (50ml). The mixture was stirred rapidly for 4 hours and concentrated *in vacuo*. The residue was partitioned between water and cyclohexane. The aqueous phase was acidified with 10% citric acid and extracted with ethyl acetate. The ethyl acetate extracts were washed with brine and dried ($MgSO_4$). Concentration *in vacuo* gave the title compound (10.21g) as a colourless gum.
LC-MS (System A): Rt = 3.14min.

Description 32

A solution of the compound of Description 31 (0.75g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU", 1.08g), in anhydrous dimethylformamide (20ml) was left standing at room temperature for

5min. 1-[(3,4-Dichlorophenyl)methyl]piperazine [CAS 55513-17-2] (0.9g) and diisopropylethylamine (1.47ml) were added and the resulting mixture was left standing at room temperature overnight. The solvent was removed *in vacuo*. Chromatographic purification of the crude product mixture on silica (Varian Bond-Elut™, 20g), eluting with 2:3 ethyl acetate/cyclohexane, gave the title compound (1.2g) as a white glass.
LC-MS (System A): Rt = 3.48min.

Description 33

A solution of the compound of Description 32 (1.2g) in tetrahydrofuran (20ml) was treated with a 1.0M solution of borane/THF complex in THF (12.2ml) and the resulting mixture was heated at 65°C for 12 hours. The cooled mixture was quenched with methanol (10ml). 2M hydrochloric acid (20ml) was added and the mixture was stirred for 1 hour then neutralised with solid sodium bicarbonate. The reaction mixture was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 20g), eluting with a gradient of ethyl acetate/cyclohexane, gave the title compound (0.18g) from 1:2 ethyl acetate:cyclohexane as a colourless oil.
LC-MS (System A): Rt = 3.11min.

Description 34

A solution of the compound of Description 33 (0.12g) in dichloromethane (10ml) was treated with a (1:1) mixture of trifluoroacetic acid and dichloromethane (2ml). The reaction mixture was left at room temperature for 2 hours. The mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and sodium bicarbonate. The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (0.082g) as a colourless gum.
LC-MS (System A): Rt = 3.12min.

Synthetic Method L

Example 30

A solution of the compound of Description 38 (0.077g) in propan-2-ol (3ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.022ml) and diisopropylethylamine (0.034ml) and the resulting solution was heated under reflux overnight. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate followed by methanol/ethyl acetate (9:1), gave a yellow oil. Further purification by automated preparative HPLC gave the title compound (0.024g) as a yellow oil.
LC-MS (System A): Rt = 2.72min. Mass Spectrum *m/z* 510 [MH^+].

The starting material for Example 30 may be prepared according to Descriptions 35-38 below.

Description 35

A solution of 4-amino-D-phenylalanine hydrate [102281-45-8] (1g) in dimethylformamide (20ml) was treated with diisopropylethylamine (0.88ml). After 5 minutes the reaction mixture was treated with Di-tert-butyl dicarbonate (2.75g) and dimethylaminopyridine (0.062g) and the resulting mixture was stirred overnight. The solution was concentrated *in vacuo*. The residue was suspended in (1:1) isopropanol/water (100ml) and further treated with 2.0M sodium hydroxide (2.5ml) and Di-tert-butyl dicarbonate (2.75g). The resulting solution was stirred for 2h. The reaction solution was treated with citric acid until a suspension was formed. The suspension was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (1.57g) as a yellow foam.
LC-MS (System A): Rt = 3.26min.

Description 36

A mixture of the compound of Description 35 (1.07g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU", 1.07g) in anhydrous dimethylformamide (10ml) was left standing at room temperature for 5min. The resulting solution was then treated with 1-[(3,4-dichlorophenyl)methyl] piperazine [CAS 55513-17-2] (0.9g) and diisopropylethylamine (1.72ml). The resulting mixture was left standing at room temperature for 3 days. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (30ml) and saturated sodium bicarbonate (30ml). The organic phase was sequentially washed with saturated sodium bicarbonate (30ml) and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (1.64g) as an orange foam.
LC-MS (System A): Rt = 3.60min.

Description 37

A solution of the compound of Description 36 (1.6g) in tetrahydrofuran (20ml) was treated with a 1.0M solution of Borane/THF complex in THF (15.8ml) and the resulting mixture was stirred at room temperature overnight. The mixture was quenched with methanol and stirred for 1h then concentrated *in vacuo*. Chromatographic purification on silica (Biotage™, 40g), eluting with a gradient of ethyl acetate/cyclohexane followed by methanol/ethyl acetate (9:1), gave the title compound (0.237g) as a white solid.

LC-MS (System A): Rt = 3.15min.

Description 38

The compound of Description 37 (0.237g) was suspended in a 4.0M solution of HCl in dioxan (5ml) and the resulting mixture was stirred at room temperature for 4h. The mixture was concentrated *in vacuo*. The residue was dissolved in dichloromethane and sequentially washed with saturated sodium bicarbonate (x2) and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (0.153g) as a yellow oil.

LC-MS (System A): Rt = 1.84min.

Synthetic Method M

Example 31

A solution of the compound of Description 41 (0.056g) in propan-2-ol (3ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.012ml) and diisopropylethylamine (0.072ml) and the resulting solution was heated under reflux overnight. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate followed by methanol/ethyl acetate (9:1), gave the title compound (0.04g) as a yellow oil.

LC-MS (System A): Rt = 2.85min. Mass Spectrum *m/z* 552 [MH^+]

The starting material for Example 31 may be prepared according to Descriptions 39-41 below.

Description 39

A solution of the compound of Description 38 (0.091g) in propan-2-ol (5ml) was treated with di-tert-butyl dicarbonate (0.05g) and triethylamine (0.031ml) and the resulting solution was stirred at room temperature for 4h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.051g) as a white foam.

LC-MS (System A): Rt = 2.64min.

Description 40

A solution of the compound of Description 39 (0.053g) in pyridine (2ml) was treated with acetic anhydride (0.01ml) and the resulting solution was stirred at room temperature for 4h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a

gradient of cyclohexane/ethyl acetate, gave the title compound (0.047g) as a colourless oil.
LC-MS (System A): Rt = 2.79min.

Description 41
The compound of Description 40 (0.047g) was suspended in a 4.0M solution of HCl in dioxan (2ml) and the resulting mixture was left to stand overnight. The mixture was concentrated *in vacuo* to give the title compound (0.059g) as a yellow solid.
LC-MS (System A): Rt = 2.09min.

Synthetic Method N
Example 32
A solution of the compound of Description 42 (0.058g) in propan-2-ol (2ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.016ml) and diisopropylethylamine (0.021ml) and the resulting solution was heated under reflux for 24h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate followed by methanol/ethyl acetate (9:1), gave the title compound (0.015g), from ethyl acetate/cyclohexane (1:1), as a white solid.
LC-MS (System A): Rt = 3.15min. Mass Spectrum *m/z* 606 [MH^+]

The starting material for Example 32 may be prepared according to Description 42 below.

Description 42
A solution of the compound of Description 37 (0.19g) in dichloromethane (5ml) was treated with trifluoroacetic acid (5ml) and the resulting solution was heated under reflux for 4h. The solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (30ml) and the solution was sequentially washed with saturated sodium bicarbonate (x2) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.063g) as a colourless oil.
LC-MS (System A): Rt = 2.58min.

Synthetic Method O
Example 39
A solution of 4-[(3,4-dichlorophenyl)methyl]-α-(1-methylethyl)-(αR)-1-piperazineethanamine [CAS 220772-44-1] (0.05g) in xylene (3ml) was treated

with 5-methyl-benzoxazole-2(3H)-thione [CAS 22876-22-8] (0.0248g) and the resulting solution was heated at 140°C for 2.5h. The solution was concentrated by vacuum centrifuge. Chromatographic purification of the residue on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.018g) as a yellow gum.
LC-MS (System A): Rt = 3.29min. Mass Spectrum *m/z* 461[MH^+]

Synthetic Method P
Example 52

A solution of Example 1 (0.08g) in dimethylformamide (1ml) was treated with sodium hydride (0.0047g). The reaction mixture was stirred for 15min. Methyl iodide (0.025g) was added. After stirring for 18h at room temperature the solution was concentrated *in vacuo*. The mixture was dissolved in ethyl acetate (20ml), washed with water (20ml), dried ($MgSO_4$) and evaporated. Purification by automated preparative HPLC gave the title compound (0.004g) as a yellow gum.
LC-MS (System A): Rt = 3.22min. Mass Spectrum *m/z* 462[MH^+]

Synthetic Method R
Example 54

Example 15 (prepared from fmoc-D-ser(tbu)-OH [CAS128107-47-1] using Synthetic Method B) (0.02g) was dissolved in a 4M solution of hydrogen chloride in dioxan (1ml). The reaction mixture was left to stand at room temperature for 4h then concentrated and dried *in vacuo* to give the title compound (0.018g) as a cream solid.
LC-MS (System A): Rt = 2.70min. Mass Spectrum *m/z* 435[MH^+]

Synthetic Method S
Example 62

N-α-Fmoc-N-im-trityl-D-histidine [CAS 135610-90-1] was converted, in four steps using Synthetic Method B, into the [imidazole N-(triphenylmethyl)] protected analogue of Example 62. This intermediate (0.095g) was treated with a mixture of trifluoroacetic acid (1ml) and dichloromethane (0.5ml). The mixture was left to stand overnight then concentrated *in vacuo*. The residue was partitioned between dichloromethane (5ml) and saturated aqueous sodium bicarbonate (5ml). The organic phase was washed with brine (5ml), dried ($MgSO_4$) and concentrated *in vacuo*. Autoprep. HPLC purification gave the title compound (0.054g) as a colourless oil.
LC-MS (System A): Rt = 2.40min. Mass Spectrum *m/z* 485[MH^+].

Synthetic Method T

Example 63

A solution of the compound of Description 45 (0.12g) in dichloromethane (1ml) was treated with a (1:1) mixture of trifluoroacetic acid and dichloromethane (1ml). The reaction mixture was left to stand for 3 hours. The mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane and sodium bicarbonate. The organic phase was separated, dried ($MgSO_4$) and concentrated. The residue was purified on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate and then methanol/ethyl acetate, to give the title compound (0.035g), from 10% methanol in ethyl acetate, as a colourless gum.

LC-MS (System A): Rt = 2.29min. Mass Spectrum *m/z* 449[MH^+]

The starting material for Example 63 may be prepared according to Descriptions 43-45 below.

Description 43

A solution of fmoc D-ser(tBu)-OH [CAS 128107-47-1] (7.45g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU", 7.4g) in anhydrous dimethylformamide (30ml) was left to stand at room temperature for 10min. The resulting solution was then treated with 1-[(3,4-dichlorophenyl)methyl] piperazine [CAS 55513-17-2] (6.2g) and diisopropylethylamine (11.8ml). The resulting mixture was left to stand at room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (90g Biotage), eluting with 1:1 cyclohexane/ethyl acetate, gave the title compound (13.85g) as a yellow foam.

LC-MS (System A): Rt = 3.83min.

Description 44

A solution of the compound of Description 43 (6.6g) in tetrahydrofuran (40ml) was treated with a 1.0M solution of Borane/THF complex in THF (65ml) and the resulting mixture was stirred for 3 days. The reaction mixture was cooled and quenched by careful addition of methanol (100ml). 2M Hydrochloric acid (5ml) was added and the mixture was stirred for 30min then neutralised with sodium bicarbonate and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification of the residue on silica (90g

Biotage), eluting with a gradient of ethyl acetate/methanol/triethylamine, gave the title compound (1.9g) from 10% triethylamine/methanol as a colourless oil.
LC-MS (System A): Rt = 2.12min.

Description 45
A solution of the compound of Description 44 (0.148g) in propan-2-ol (5ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.087ml) and triethylamine (0.053ml) and the resulting solution was heated under reflux for 18h. The solution was cooled and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.126g), from ethyl acetate/cyclohexane (1:1), as a colourless gum.
LC-MS (System A): Rt = 2.98min.

Synthetic Method U
Example 65
Array to give Examples 65-71
Equal (*ca* 1ml) portions of a mixture of the compound of Description 47 (0.28g) and diisopropylethylamine (0.2ml) in dichloromethane(9ml) were dispensed into 9 scintillation vials and each was treated with the appropriate amine[1], followed by a solution of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ["HATU", 1ml from a stock solution of 0.24g in dimethylformamide (9ml)]. The mixtures were left to stand overnight then concentrated *in vacuo* and partitioned between dichloromethane (5ml) and saturated aqueous sodium bicarbonate (5ml). The organic phases were separated through hydrophobic frits. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate followed by methanol and 1% triethylamine, gave the title compounds from 9:1 ethyl acetate: methanol:1%Et_3N.

Example 65
Obtained as a light brown gum (0.026g) ([1]from glycine methyl ester).
LC-MS (System A): Rt = 2.54min. Mass Spectrum *m/z* 520[MH^+].

The starting material for Example 65 may be prepared according to Descriptions 46-47 below.

Description 46
The compound of Description 10 (1.4g) was treated with 6M aqueous hydrochloric acid (30ml). The reaction mixture was heated at 70°C for 1.5h,

cooled and concentrated. The residue was dried *in vacuo* to give the title compound (1.20g) as a brown solid.
LC-MS (System A): Rt = 1.55min.

Description 47
A mixture of the compound of Description 46 (1.2g), 2-chlorobenzoxazole [CAS 615-18-9] (0.7ml) and triethylamine (2.12ml) in propan-2-ol (20ml) was heated at 70°C overnight. The reaction mixture was cooled and concentrated *in vacuo*. The residue was purified on silica (Varian Bond-Elut™, 50g), eluting with a gradient of cyclohexane/ethyl acetate followed by methanol, to give the impure product from (2:1) ethyl acetate:methanol . This material was partitioned between chloroform and water. The chloroform phase was concentrated *in vacuo* to give the title compound (0.35g) as a brown foam.
LC-MS (System A): Rt = 2.80min.

Synthetic Method V
Synthetic Method V incorporates examples of a variety of methods that were used to interconvert compounds of formula (I), by chemical modification of R^3 [process (g)].

Example 84
A solution of morpholine (0.100g) in acetonitrile (1ml) was added to a stirred suspension of Example 58 (prepared from fmoc-D-glu(OtBu)-OH [CAS 104091-08-9] using Synthetic Methods C and R) (0.050g) in acetonitrile, followed immediately by the addition of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU", 0.050g). The reaction mixture was stirred for 2.5h then left to stand overnight. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (15ml) and 0.5M sodium bicarbonate (10ml). The organic phase was separated, washed with 0.25M sodium bicarbonate (10ml) and water (10ml), dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless glass. Salt formation (1.0M hydrogen chloride in ether) gave the title compound (0.042g) as a white powder.
LC-MS (System A): Rt = 2.70min. Mass Spectrum *m/z* 546[MH^+].

Example 95
A solution of Example 54 (0.050g) in anhydrous dimethylformamide (3ml) was treated with sodium hydride (0.005g). The reaction mixture was stirred for 15min. Methyl bromoacetate (0.011ml) was added. After stirring for 24h at room temperature the solution was concentrated *in vacuo*. The mixture was partitioned between dichloromethane (10ml) and water. The organic phase was separated,

dried ($MgSO_4$) and evaporated. Purification by automated preparative HPLC chromatography gave the title compound (0.0057g) as colourless oil.
LC-MS (System A): Rt = 2.23min. Mass Spectrum *m/z* 507[MH^+].

Example 101

A solution of Example 25 (prepared from (4-hydroxybutyl)glycine [CAS 305-77-1] using Synthetic Method F) (0.038g), triphenylphosphine (0.028g) and glacial acetic acid (0.007g) in tetrahydrofuran (2ml) was stirred for 2min. Diisopropylazodicarboxylate (0.020g) was added and the reaction mixture was stirred for 4h. More glacial acetic acid (0.010g) was added and stirring was continued for 3h. The reaction mixture was left to stand overnight then concentrated *in vacuo*. Chromatographic purification of the residue on silica (Varian Bond-Elut™, 10g), eluting with a (1:1) mixture of ethyl acetate and cyclohexane, gave a colourless glass. Salt formation (1.0M hydrogen chloride in ether) gave the title compound (0.007g) as a cream powder.
LC-MS (System A): Rt = 2.88min. Mass Spectrum *m/z* 519[MH^+].

Example 104

A solution of Example 57 (prepared from fmoc-D-lys(boc)-OH [CAS 92122-45-7] using Synthetic Methods C and R) (0.05g) in dichloromethane (5ml) was treated with methanesulphonyl chloride (0.008ml) and triethylamine (0.014ml) and the resulting solution was stirred at room temperature for 5h. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with ethyl acetate/cyclohexane (1:1), ethyl acetate and ethyl acetate/methanol (9:1), gave the title compound (0.023g) from ethyl acetate/methanol (10:1) as a pale yellow oil.
LC-MS (System A): Rt 2.82min. Mass Spectrum *m/z* 554 [MH^+].

Example 108

A solution of the compound of Description 48 (0.027g), glacial acetic acid (0.015g) and N-methyl glycine tert-butyl ester [CAS 5616-81-9] (0.020g) in dichloromethane (3.7ml) was stirred for 10min. Sodium triacetoxyborohydride (60mg) was added and stirring was continued for 1.5h. The reaction mixture was left to stand overnight. Sodium bicarbonate (1.0M, 5ml) was added, with stirring. After stirring for 5 min the mixture was partitioned between water (5ml) and dichloromethane (10ml). The aqueous phase was separated and extracted with dichloromethane (10ml). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a gum. Chromatographic purification of the gum on silica (Varian Bond-Elut™, 10g), eluting initially with ethyl acetate and then with a (100:8:1) mixture of dichloromethane, ethanol and ammonia, gave the title

compound (0.021g), from a (100:8:1) mixture of dichloromethane, ethanol and ammonia, as a colourless gum.
LC-MS (System A): Rt = 2.53min. Mass Spectrum *m/z* 590[MH^+]

The starting material for Example 108 may be prepared according to Description 48 below.

Description 48
A solution of dimethylsulphoxide (0.056g) in dichloromethane (1ml) was added to a stirred solution of oxalyl chloride (0.045g) in dichloromethane (1ml) at –70°C. The resultant solution was stirred at –60°C to –70°C for 10min then a solution of Example 22 (0.085g) in dichloromethane (4ml) was added over 3 min. The reaction mixture was stirred at –40°C to –70°C for 1.25h. Diisopropylethylamine (0.129g) was added and the reaction mixture was warmed to +5°, with stirring, over 1h. The reaction mixture was partitioned between 0.5M sodium bicarbonate (10ml) and dichloromethane (20ml). The aqueous phase was extracted with dichloromethane (10ml). The combined organics were washed with water (15ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.074g) as a pale brown gum.
LC-MS (System A): Rt = 2.74min.

Example 117
A solution of 4.0M hydrogen chloride in dioxan (0.2ml) was added to a stirred solution of Example 108 (0.015g) in dioxan (1.5ml). The reaction mixture was stirred for 19h then concentrated *in vacuo*. The residue was washed with diethyl ether, then dried *in vacuo* to give the title compound (0.015g) as a yellow powder.
LC-MS (System A): Rt = 2.51min. Mass Spectrum *m/z* 534[MH^+]

Example 121
A solution of sodium periodate (0.009g) in water (1.5ml) was added to a stirred solution of Example 19 (0.023g) in methanol (4ml) at 0-5°. The reaction mixture was stirred at 0-10° for 2h. Sodium bicarbonate (2g) was added, followed by ethyl acetate (15ml). The suspension was filtered. The filtrate was concentrated to give an oil. A solution of the oil in ethyl acetate (10ml) was dried (Na_2SO_4) and concentrated *in vacuo* to give a gum. Salt formation (1.0M hydrogen chloride in ether) gave the title compound (0.018g) as a yellow powder.
LC-MS (System A): Rt = 2.66min. Mass Spectrum *m/z* 495[MH^+]

Example 124

A solution of Example 57 (prepared from fmoc-D-lys(boc)-OH [CAS 92122-45-7] using Synthetic Methods C and R) (0.037g) in dichloromethane (2ml) was treated with 4-nitrophenyl chloroformate (0.032g) and triethylamine (0.026ml). After 1h, 2.0M methylamine in THF (0.2ml) was added and the reaction mixture was left overnight. The reaction mixture was partitioned between dichloromethane (30ml) and saturated sodium bicarbonate (30ml). The organic phase was separated and washed further with saturated sodium bicarbonate (6 x 30ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica (Varian Bond-Elut™, 5g), eluting with a gradient of ethyl acetate/cyclohexane followed by methanol/ethyl acetate (9:1), to give a yellow oil. Further purification by automated preparative HPLC gave the title compound (0.008g) as a colourless oil.

LC-MS (System A): Rt = 2.78min. Mass Spectrum *m/z* 533 [MH^+]

Example 125

A solution of Example 57 (prepared from fmoc-D-lys(boc)-OH [CAS 92122-45-7] using Synthetic Methods C and R) (0.021g) in propan-2-ol (2ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.006ml) and diisopropylethylamine (0.008ml) and the resulting solution was heated under reflux for 18h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate followed by methanol/ethyl acetate (9:1), gave the title compound (0.015g) as a colourless oil.

LC-MS (System A): Rt = 3.14min. Mass Spectrum *m/z* 593 [MH^+]

Synthetic Method W

Example 111

A solution of the compound of Description 53 (0.040g), 1-[(3,4-dichlorophenyl)methyl]piperazine [CAS 55513-17-2] (0.062g) and glacial acetic acid (0.030g) in dichloromethane (5ml) was stirred for 5min. Sodium triacetoxyborohydride (0.063g) was added. The reaction mixture was stirred for 4.0h. More sodium triacetoxyborohydride (0.063g) and glacial acetic acid (0.012g) were added. The reaction mixture was stirred for a further 1.5h. Sodium bicarbonate (5ml) was added. The reaction mixture was extracted with dichloromethane (10ml + 5ml). The combined organics were washed with water (10ml), dried (Na_2SO_4) and concentrated *in vacuo* to give a gum. Chromatographic purification of the gum on silica (Varian Bond-Elut™, 5g), using ethyl acetate as the eluent, gave a colourless gum. Salt formation (1.0M

hydrogen chloride in diethyl ether) gave the title compound (0.039g) as a white powder.
LC-MS (System A): Rt = 2.94min. Mass Spectrum *m/z* 547[MH^+]

The starting material for Example 111 may be prepared according to Descriptions 49-53 below.

Description 49

Di-tert-butyl dicarbonate (0.272g) was added to a solution of 2-aminooctanedioic acid, 8-ethyl ester [methyl ester: CAS 131956-96-2] (0.203g) and diisopropylethylamine (0.258g) in tetrahydrofuran (12ml) and water (12ml), with stirring. The reaction mixture was stirred for 6h, left to stand for 2 days then concentrated to 10ml *in vacuo*. Citric acid (6ml) was added. The resultant suspension was extracted with ethyl acetate (2x20ml). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.279g) as a colourless, viscous oil.
^1H NMR δ ($CDCl_3$) 5.0 (1H, d), 4.3 (1H, q), 4.1 (2H, q), 2.3 (2H, t), 1.9-1.5 (4H, m), 1.45 (9H, s), 1.5-1.3 (4H, m), 1.3 (3H, t).

Description 50

A solution of the compound of Description 49 (0.090g) in tetrahydrofuran (5ml) and a 1.0M solution of borane/THF complex in THF (1.0ml) was stirred at 0-5° for 0.5h then treated with methanol (2ml), with stirring. The reaction mixture was concentrated to give a gum. The gum was partitioned between ethyl acetate (20ml) and 0.5M sodium carbonate (15ml). The organic phase was separated, washed with 0.5M sodium carbonate (15ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.035g) as a pale yellow gum.
Tlc (Silica, ethyl acetate:cyclohexane 1:1). Rf = 0.38. $KMnO_4$ detection.

Description 51

A 4.0M solution of hydrogen chloride in dioxan (0.5ml) was added to a stirred solution of the compound of Description 50 (0.088g) in dioxan (5ml). The reaction mixture was stirred for 16h. More hydrogen chloride in dioxan (4.0M, 0.5ml) was added. The reaction mixture was stirred for a further 8h then concentrated *in vacuo*. The residual glass was triturated in diethyl ether to give a solid. The ether was decanted and the solid was dried *in vacuo* to give the title compound (0.061g) as a yellow solid.
Tlc [Silica, dichloromethane:ethanol:ammonia (100:8:1)]. Rf = 0.1. $KMnO_4$ detection.

Description 52

A mixture of the compound of Description 51 (0.060g), 2-chlorobenzoxazole [CAS 102-47-6] (0.060g) and diisopropylethylamine (0.129g) in propan-2-ol (15ml) was heated at reflux for 6.5h, cooled and concentrated *in vacuo* to leave a viscous oil. Chromatographic purification of the oil on silica (Varian Bond-Elut™, 5g), eluting initially with a (1:1) mixture of ethyl acetate and cyclohexane and then with ethyl acetate, gave the title compound (0.055g) from ethyl acetate as a pale yellow gum.

LC-MS (System A): Rt = 2.92min.

Description 53

A solution of dimethylsulphoxide (0.056g) in dichloromethane (1ml) was added to a stirred solution of oxalyl chloride (0.045g) in dichloromethane (1ml) at –70°C. The resultant solution was stirred at –60°C to –70°C for 10min then a solution of the compound of Description 52 (0.052g) in dichloromethane (4ml) was added over 2 min. The reaction mixture was stirred at –40°C to –70°C for 1.25h. Diisopropylethylamine (0.129g) was added and the reaction mixture was warmed to +10°, with stirring, over 0.75h. The reaction mixture was partitioned between 0.5M sodium bicarbonate (6ml) and dichloromethane (10ml). The aqueous phase was extracted with dichloromethane (5ml). The combined organics were washed with water (15ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.044g) as a yellow gum.

Tlc (Silica, ethyl acetate). Rf = 0.78. UV and $KMnO_4$ detection.

Synthetic Method X

Example 129

A solution of the compound of Description 54 (0.017g) and the compound of Description 56 (0.019g) in dichloromethane (3ml) containing glacial acetic acid (0.010g) was stirred for 10min then treated with sodium triacetoxyborohydride (0.043g). The reaction mixture was stirred for 1.5h then 1.0M sodium bicarbonate (5ml) was added, with vigorous stirring. The reaction mixture was extracted with dichloromethane (2x10ml). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residual glass was purified by chromatography on silica (Varian Bond-Elut™, 5g), eluting with a mixture of dichloromethane, ethanol and ammonia (100:8:1), to give a glass. Salt formation (1.0M hydrogen chloride in ether) gave the title compound (0.008g) as white needles.

LC-MS (System A): Rt 3.57, 3.62 min. (diastereoisomers). Mass Spectrum *m/z* 490 [MH^+]

The starting materials for Example 129 may be prepared according to Descriptions 54-56 below.

Description 54

A mixture of 2-piperazinecarboxamide [CAS 84501-64-4] (0.53g), 3,4-dichlorobenzyl chloride [CAS 102-47-6] (0.57ml) and sodium bicarbonate (0.35g) in ethanol (20ml) was heated at reflux for 3 days. The suspension was cooled and filtered. The filtrate was concentrated and the resultant residue was partitioned between 1.0M hydrochloric acid (10ml) and dichloromethane (2x25ml). The aqueous phase was separated, basified to pH13 with 2.0M sodium hydroxide and extracted with dichloromethane (2x25ml). These latter organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.23g) as a yellow foam.
LC-MS (System A): Rt = 2.40min.

Description 55

A mixture of 2-chlorobenzoxazole [CAS 615-18-9] (0.46g), (DL)-2-amino-3-methyl-1-butanol [CAS 16369-05-4] (0.21g) and diisopropylethylamine (0.52g) in isopropanol (30ml) was stirred and heated at reflux for 7h. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate (30ml) and 1.0M sodium bicarbonate (15ml). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to give a solid. The solid was triturated in diethyl ether (12ml). The solvent was decanted and the residue was dried *in vacuo* to give the title compound (0.32g) as a white solid.
LC-MS (System A): Rt = 2.72min.

Description 56

A solution of dimethylsulphoxide (0.35g) in dichloromethane (5ml) was added, rapidly dropwise, to a stirred solution of oxalyl chloride (0.28g) in dichloromethane (5ml), the temperature of the reaction mixture being maintained between –60°C and –70°C during the addition. The reaction mixture was stirred at –60°C to –70°C for 0.25h then a solution of the compound of Description 55 (0.44g) in dichloromethane (10ml) was added, rapidly dropwise over 2-3 min. The reaction mixture was stirred at –50°C to –70°C for 20min. Diisopropylethylamine (1.29g) was added and the solution was warmed to 20°C with vigorous stirring. The reaction mixture was partitioned between dichloromethane (20ml) and 0.5M sodium bicarbonate (20ml). The aqueous phase was separated and extracted with dichloromethane (20ml). The combined organic extracts were washed with water (30ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica

(Varian Bond-Elut™, 20g), eluting with cyclohexane and ethyl acetate (1:1), to give the title compound (0.16g) as a white solid.
LC-MS (System A): Rt = 3.73min.

Synthetic Method Y

Example 133

1.0ml of a 0.05M stock solution of the compound of Description 63 in dichloromethane was treated with diisopropylethylamine (0.2ml) followed by 3-chlorobenzyl bromide (7.2µl) and the resulting mixture was left to stand at room temperature for 18h. Chromatographic purification of the mixture on silica (Varian Bond-Elut™), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (0.017g) from ethyl acetate as a buff solid.
LC/MS (SystemA): Rt = 2.49min. Mass Spectrum *m/z* 444 [MH^+].

The starting material for Example 133 may be prepared according to Descriptions 57-63 below.

Description 57

DL-2-Amino-3-methyl-1-butanol [CAS 16369-05-4] (20g) was stirred in methanol (500ml) and triethylamine (50ml) and the resulting solution was treated, in portions, with di-tert-butyl dicarbonate (53.5g) over 2.5h at room temperature. The mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (400ml) and 2M hydrochloric acid (200ml). The organic phase was sequentially washed with 2M hydrochloric acid (200ml), water and brine, dried ($MgSO_4$) and concentrated. Chromatographic purification on silica (Merck 9385), eluting first with chloroform then with chloroform/methanol (19:1), gave the title compound (32.6g) as a white solid.
LC/MS (System A): Rt = 2.60min.

Description 58

The compound of Description 57 (22.4g) was dissolved in anhydrous dichloromethane (300ml) and the solution was cooled in an ice bath and stirred under nitrogen. The cooled mixture was treated with triethylamine (19.9ml) and methanesulphonyl chloride (10.2ml). The resulting white suspension was stirred at 0°C for 1h and then at room temperature for 0.5h. The mixture was sequentially washed with water, aqueous citric acid, water and brine, dried ($MgSO_4$) and concentrated to give the title compound (29.85g) as a white solid.
Tlc (Silica, chloroform/methanol [19:1]): Rf = 0.61 (anisaldehyde stain).

Description 59

The compound of Description 58 (19.1g) was dissolved in anhydrous tetrahydrofuran (80ml) and the solution was added to a stirred suspension of piperazine (58.4g) and diisopropylethylamine (11.8ml) in tetrahydrofuran (160ml). The resulting suspension was heated under reflux for 2h. The cooled suspension was filtered and the residual solid washed with tetrahydrofuran. The filtrate was concentrated *in vacuo*. Chromatographic purification on silica (Merck 9385), using 2% Et_3N in methanol/chloroform (19:1) as the eluent, gave the title compound (11.8g) as a straw coloured oil.
LC/MS (System A): Rt = 2.00min.

Description 60

The compound of Description 59 (11.8g) in tetrahydrofuran (15ml) and water (30ml) was treated with 2M aqueous sodium carbonate (21.75ml) to give pH 10. The resulting solution was cooled to 0°C and treated slowly with allyl chloroformate (4.62ml), maintaining the temperature below 5°C. The resulting cooled mixture was further treated with 2M sodium carbonate (10.9ml) and stirred for 1h at 5°C and then at room temperature for 18h. The reaction mixture was extracted with diethyl ether (2x50ml). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (90g Biotage column), eluting with cyclohexane/ethyl acetate (9:1 then 4:1), gave the title compound (12.6g) as a colourless oil.
Tlc [Silica, chloroform/methanol (19:1)]: Rf = 0.49.

Description 61

A solution of the compound of Description 60 (47.1g) in 1,4-dioxan (300ml) was treated with a 4M solution of HCl in dioxan (280ml). The resulting mixture was stirred at room temperature for 4h. The mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (500ml) and extracted with 2M hydrochloric acid (3x500ml). The combined aqueous layers were washed with dichloromethane and ethyl acetate then made basic with 2M sodium hydroxide. The basic phase was extracted with ethyl acetate (x2). The combined ethyl acetate extracts were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (30.9g) as a colourless oil.
LC/MS (System A): Rt = 2.05min.

Description 62

A solution of the compound of Description 61 (2.8g) in propan-2-ol (5ml) was treated with 7-chloro-3-methylthieno[3,2-d]pyrimidine [CAS 175137-21-0] (3.5g) and diisopropylethylamine (0.06ml) and the resulting solution was heated under

reflux for 18h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (2.49g) as a white solid.
LC/MS (System A): Rt = 2.04min.

Description 63

A solution of the compound of Description 62 (0.58g) in anhydrous tetrahydrofuran (35ml) was treated with diethylamine (2.2ml) and tetrakis(triphenylphosphine)palladium(0) (0.2g). The resulting mixture was stirred at room temperature for 1h. The mixture was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 10g), eluting with ethyl acetate/methanol gradient, gave the title compound (0.41g) from methanol/1%Et_3N as a white solid.
LC/MS (System A): Rt = 1.83min.

Synthetic Method Z

Example 134

A solution of the compound of Description 68 (0.05g) in dichloromethane (5ml) was treated with triethylamine (0.044ml) and 3,4-difluorobenzyl bromide (0.0104ml) and the resulting solution was stirred at room temperature overnight. Chromatographic purification of the crude mixture on silica (Varian Bond-Elut™, 5g), eluting with a gradient of cyclohexane/ethyl acetate followed by methanol/ethyl acetate (9:1), gave the title compound (0.019g) as an orange oil.
LC-MS (System A): Rt = 2.43min. Mass Spectrum *m/z* 403 [MH^+]

The starting material for Example 134 may be prepared according to Descriptions 64-68 below.

Description 64

A mixture of Z-D-Ser(tBu)-OH [CAS 65806-90-8] (5.1g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU", 6.46g) in anhydrous dimethylformamide (20ml) was left to stand at room temperature for 5min. The resulting solution was then treated with 1-BOC-piperazine [CAS 57260-71-6] (3.22g) and diisopropylethylamine (4.4ml). The resulting mixture was left to stand at room temperature overnight. The solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (30ml) and the solution was sequentially washed with saturated sodium bicarbonate (x2) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Biotage™, 90g), eluting with cyclohexane/ethyl acetate (4:1), gave the title compound (3.5g) as a yellow oil.

LC-MS (System A): Rt = 3.60min.

Description 65

A solution of the compound of Description 64 (6.7g) in ethyl acetate (100ml) and propan-2-ol (100ml) was hydrogenated at room temperature and atmospheric pressure, using 10% Palladium on activated carbon as the catalyst. On completion of the reaction the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give the title compound (5.18g) as a colourless oil.
LC-MS (System A): Rt = 2.28min.

Description 66

A solution of the compound of Description 65 (0.109g) in propan-2-ol (3ml) was treated with 2-chlorobenzoxazole [CAS 102-47-6] (0.045ml) and diisopropylethylamine (0.057ml) and the resulting solution was heated under reflux overnight. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 10g), eluting with cyclohexane/ethyl acetate (1:1), gave the title compound (0.117g) as a colourless oil.
LC-MS (System A): Rt = 3.38min.

Description 67

A solution of the compound of Description 66 (0.109g) in tetrahydrofuran (5ml) was treated with a 1.0M solution of Borane/THF complex in THF (1.47ml) and the resulting mixture was heated under reflux overnight. The mixture was cooled, quenched with methanol and stirred for 1h then concentrated *in vacuo*. Chromatographic purification of the residue on silica (Varian Bond-Elut™, 10g), eluting with cyclohexane/ethyl acetate (4:1) and cyclohexane/ethyl acetate (1:1), gave the title compound (0.05g) as a yellow oil.
LC-MS (System A): Rt = 2.79min.

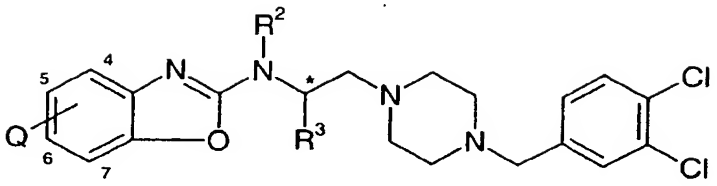
Description 68

A solution of the compound of Description 67 (0.05g) in dichloromethane (4ml) was treated with trifluoroacetic acid (2ml) and the resulting solution was left to stand at room temperature for 24h. The solvent was removed *in vacuo* to give the title compound (0.05g) as a brown oil.
LC-MS (System A): Rt = 1.22min.

In addition to the Examples disclosed above, further Examples of the invention are given in Tables 1 to 4. The further Examples described therein were prepared by analogy to Synthetic Methods A to Z disclosed above. The

reference to the analogous Synthetic Method used for any Example is also provided in Tables 1 to 4.

Table 1



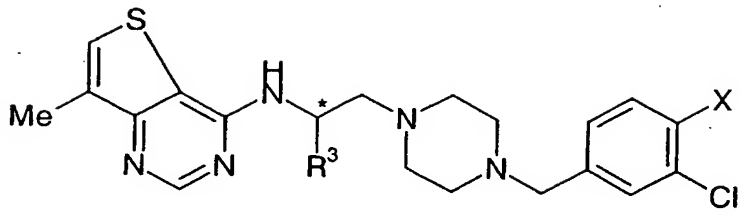
Ex. No.	Synthetic Method	Q	R^2	Stereochem at position (*)	R^3	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) $[M+H]^+$ unless otherwise indicated
1	A	H	H	RS	$-CH(CH_3)_2$	447.41	447
2	A	H	H	R	$-CH(CH_3)_2$	447.41	447
12	B	H	H	R	$-CH_2CH(CH_3)_2$	461.44	461
13	B	H	H	R	-cyclohexyl	487.48	487
14	B	H	H	R	$-(CH_2)_3CH_3$	461.44	461
15	B	H	H	S	$-CH_2OtBu$	491.47	491
16	B	H	H	(S,S)	$-CH(CH_3)OtBu$	505.49	505
17	D	H	H	RS	$-CO_2Et$	477.39	477
18	E	H	H	R	$-(CH_2)_2OH$	449.38	449
19	F	H	H	R	$-(CH_2)_2SMe$	479.49	479
20	C	H	H	R/S (2:1)	$-CH_2CO_2tBu$	519.48	519
21	G	H	H	R/S (2:1)	$-CH_2CO_2iBu$	519.48	519
22	H	H	H	R	$-(CH_2)_3OH$	463.41	463
23	C	H	H	R	$-(CH_2)_3NHCO_2tBu$	562.54	562
24	C	H	H	R	$-(CH_2)_2CO_2tBu$	533.50	533
25	F	H	H	RS	$-(CH_2)_4OH$	477.44	477
26	C	H	H	R	$-(CH_2)_4NHCO_2tBu$	576.57	576
27	J	H	H	RS	$-(CH_2)_5NH_2$	490.48	490
28	K	H	H	R	$-CH_2Ph$	495.46	495
29	B	H	H	R	$-CH_2$(4-OtBu)Ph	567.56	567
30	L	H	H	R	$-CH_2$(4-NH_2)Ph	510.46	510
31	M	H	H	R	$-CH_2$(4-NHCOMe)Ph	552.51	552
32	N	H	H	R	$-CH_2$(4-$NHCOCF_3$)Ph	606.48	606
33	D	H	H	R	$-CH_2$(4-SO_2Me)Ph	573.55	573
38	O	4-Me	H	R	$-CH(CH_3)_2$	461.44	461

Ex. No.	Synthetic Method	Q	R^2	Stereochem at position (*)	R^3	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) $[M+H]^+$ unless otherwise indicated
39	O	5-Me	H	R	$-CH(CH_3)_2$	461.44	461
40	O	6-Me	H	R	$-CH(CH_3)_2$	461.44	461
41	O	6-iPr	H	R	$-CH(CH_3)_2$	489.49	489
42	O	5-Cl	H	R	$-CH(CH_3)_2$	481.86	481
43	O	6-Cl	H	R	$-CH(CH_3)_2$	481.86	481
44	O	7-Cl	H	R	$-CH(CH_3)_2$	481.86	481
45	O	4-F	H	R	$-CH(CH_3)_2$	465.40	465
46	O	6-F	H	R	$-CH(CH_3)_2$	465.40	465
47	O	$4-NO_2$	H	R	$-CH(CH_3)_2$	492.41	492
48	O	$5-NO_2$	H	R	$-CH(CH_3)_2$	492.41	492
49	O	$6-NO_2$	H	R	$-CH(CH_3)_2$	492.41	492
50	O	$7-NO_2$	H	R	$-CH(CH_3)_2$	492.41	492
51	O	6-Ph	H	R	$-CH(CH_3)_2$	523.51	523
52	P	H	Me	RS	$-CH(CH_3)_2$	461.43	462
53	P	H	Et	R	$-(CH_2)_2OH$	477.44	477
54	R	H	H	S	$-CH_2OH$	435.36	435
55	R	H	H	(S,S)	$-CH(CH_3)OH$	449.39	449
56	R	H	H	R	$-(CH_2)_3NH_2$	462.43	462
57	R	H	H	R	$-(CH_2)_4NH_2$	476.46	476
58	R	H	H	R	$-(CH_2)_2CO_2H$	477.40	477
59	R	H	H	R	$-CH_2$(4-OH)Ph	511.46	511
62	S	H	H	R	$-CH_2$(4-imidazolyl)	485.41	485
63	T	H	Me	S	$-CH_2OH$	449.38	449
64	R	H	H	R/S (2:1)	$-CH_2CO_2H$	463.37	463
65	U	H	H	RS	$-CONHCH_2CO_2Me$	520.42	520
66	U	H	H	RS	$-CONH(CH_2)_2OMe$	506.44	506
67	U	H	H	RS	-CONHiPr	490.44	490
68	U	H	H	RS	-CO[1-(4-CO_2tBu)piperidinyl]	616.59	616
69	U	H	H	RS	-CO(4-morpholinyl)	518.45	518
70	U	H	H	RS	$-CONMe_2$	476.41	476
71	U	H	H	RS	-CONHMe	462.38	462
72	V	H	H	R/S (2:1)	$-CH_2CONHCH_2Ph$	552.51	552
73	V	H	H	R/S (2:1)	$-CH_2$CO(4-morpholinyl)	532.47	532

Ex. No.	Synthetic Method	Q	R^2	Stereochem at position (*)	R^3	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) $[M+H]^+$ unless otherwise indicated
74	V	H	H	R/S (2:1)	-CH_2CO(1-piperidinyl)	530.50	530
75	V	H	H	R/S (2:1)	-CH_2CONH(cyclopentyl)	530.50	530
76	V	H	H	R/S (2:1)	-CH_2CO[1-(2(S)-CO_2tBu)pyrrolidinyl]	616.59	616
77	V	H	H	R/S (2:1)	-$CH_2CONHMe$	476.41	476
78	V	H	H	R/S (2:1)	-$CH_2CONHEt$	490.44	490
79	V	H	H	R/S (2:1)	-CH_2CONMe_2	490.44	490
80	V	H	H	R/S (2:1)	-$CH_2CONH(CH_2)_2OH$	506.44	506
81	V	H	H	R/S (2:1)	-CH_2CONH_2	462.39	462
82	V	H	H	R/S (2:1)	-$CH_2CONH(CH_2)_2CO_2tBu$	590.56	590
83	V	H	H	R/S (2:1)	-$CH_2CONHCH_2CO_2tBu$	576.53	576
84	V	H	H	R	-$(CH_2)_2CO$(4-morpholinyl)	546.50	546
85	V	H	H	R	-$(CH_2)_2CON[(CH_2)_2OH]_2$	564.53	564
86	V	H	H	R	-$(CH_2)_2CONH(CH_2)_5CO_2Me$	604.59	604
87	V	H	H	R	-$(CH_2)_2CONH(CH_2)_2OMe$	534.50	534
88	V	H	H	R	-$(CH_2)_2CONH(CH_2)_2O(CH_2)_2OH$	564.53	564
89	V	H	H	R	-$(CH_2)_2CON(iBu)_2$	588.64	588
90	V	H	H	R	-$(CH_2)_2CONHCH_2CO_2tBu$	590.56	590
91	V	H	H	R	-$(CH_2)_2CONH_2$	476.40	476
92	V	H	H	R	-$(CH_2)_2CONHMe$	490.43	490
93	V	H	H	R	-$(CH_2)_2CONMe_2$	504.46	504
94	V	H	H	R	-$(CH_2)_2CONHCH_2CONH_2$	533.47	533
95	V	H	H	S	-$CH_2OCH_2CO_2Me$	507.41	507
96	V	H	H	S	-CH_2OEt	463.40	463
97	V	H	H	S/R (2:1)	-$CH_2OCH_2CONH_2$	492.41	492
98	V	H	H	R	-$(CH_2)_4NHCH_2Ph$	566.57	566
99	V	H	H	R	-$(CH_2)_4N(CH_2Ph)_2$	656.71	656
100	V	H	H	R	-$(CH_2)_4NMe_2$	504.51	504
101	V	H	H	RS	-$(CH_2)_4OCOMe$	519.49	519
102	V	H	H	R	-$(CH_2)_4NHCOMe$	518.49	518
103	V	H	H	S	-CH_2OCOMe	477.39	477
104	V	H	H	R	-$(CH_2)_4NHSO_2Me$	554.54	554
105	V	H	H	R	-CH2(4-$NHSO_2Me$)Ph	588.55	588

Ex. No.	Synthetic Method	Q	R^2	Stereochem at position (*)	R^3	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) $[M+H]^+$ unless otherwise indicated
106	V	H	H	R	$-(CH_2)_3$[1-(4-$CONH_2$)piperidinyl]	573.57	573
107	V	H	H	R	$-(CH_2)_3$[1-(4-CO_2tBu)piperidinyl]	630.66	630
108	V	H	H	R	$-(CH_2)_3N(Me)CH_2CO_2$tBu	590.60	590
109	V	H	H	RS	$-(CH_2)_4$(1-piperidinyl)	544.58	544
110	V	H	H	R	(trans) $-CH_2CH=CHCO_2$tBu	545.51	545
111	W	H	H	RS	$-(CH_2)_5CO_2Et$	547.54	547
112	V	H	H	R/S (2:1)	$-CH_2CONH(4-CO_2H)Ph$	582.50	582
113	V	H	H	R/S (2:1)	$-CH_2CONH(CH_2)_2CO_2H$	534.46	534
114	V	H	H	R/S (2:1)	$-CH_2CONHCH_2CO_2H$	520.34	520
115	V	H	H	RS	$-CO$[1-(4-CO_2H)piperidinyl]	560.50	560
116	V	H	H	R	$-(CH_2)_2CONHCH_2CO_2H$	534.46	534
117	V	H	H	R	$-(CH_2)_3N(Me)CH_2CO_2H$	534.49	534
118	V	H	H	R	$-(CH_2)_3$[1-(4-CO_2H)piperidinyl]	574.56	574
119	V	H	H	R/S (2:1)	$-CH_2CO$[1-(2(S)-CO_2H)pyrrolidinyl]	560.49	560
120	V	H	H	RS	$-(CH_2)_5CO_2H$	519.49	519
121	V	H	H	R	$-(CH_2)_2S(O)Me$	495.49	495
122	V	H	H	R	$-(CH_2)_4NHCO_2Me$	534.49	534
123	V	H	H	S	$-CH_2OCONHPh$	554.48	554
124	V	H	H	R	$-(CH_2)_4NHCONHMe$	533.50	533
125	V	H	H	R	$-(CH_2)_4NH$(2-benzoxazolyl)	593.56	593
126	V	H	H	S/R (2:1)	$-CH_2OCH_2$(1-tetrazolyl)	587.39	587
127	V	H	H	R/S (2:1)	$-(CH_2)_2NH_2$	448.40	448

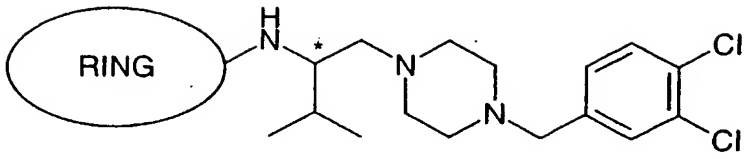
Table 2

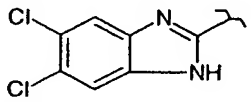
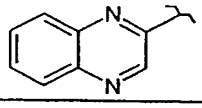
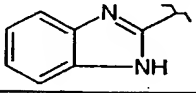
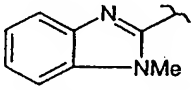
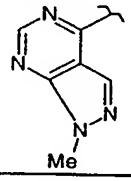
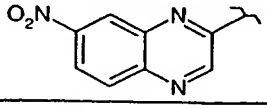
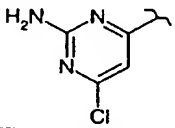
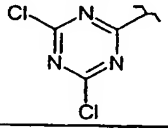


Ex. No.	Synthetic Method	Stereochem at position (*)	R^3	X	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) $[M+H]^+$ unless otherwise indicated
3	A	R	$-CH(CH_3)_2$	Cl	478.5	478
34	B	R	$-CH_2CH(CH_3)_2$	Cl	492.5	492
35	B	R	-cyclohexyl	Cl	518.6	518
36	B	S	$-CH_2OtBu$	Cl	522.5	522
37	B	(S,S)	$-CH(CH_3)OtBu$	Cl	536.6	536
60	R	S	$-CH_2OH$	Cl	466.4	466
61	R	(S,S)	$-CH(CH_3)OH$	Cl	480.5	480
133	Y	RS	$-CH(CH_3)_2$	H	444.0	444

5

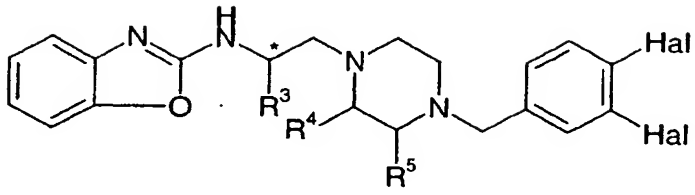
Table 3



Ex. No.	Synthetic Method	Stereochem at position (*)	RING	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) $[M+H]^+$ unless otherwise indicated
4	A	RS		515.3	516
5	A	RS		458.4	458
6	A	RS		446.3	446
7	A	RS		460.4	460
8	A	RS		462.4	462
9	A	RS		503.4	503
10	A	RS		457.8	457
11	A	R		478.3	477

5

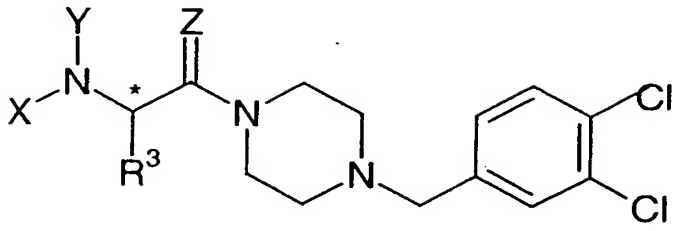
Table 4



Ex. No.	Synthetic Method	Stereochem at position (*)	R^3	R^4	R^5	Hal	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) $[M+H]^+$ unless otherwise indicated
128	X	RS	$-CH(CH_3)_2$	H	Me	Cl	461.4	461
129	X	RS	$-CH(CH_3)_2$	H	$-CONH_2$	Cl	490.5	490
130	X	R	$-CH(CH_3)_2$	H	$-CONH_2$	Cl	490.5	490
131	X	R	$-CH(CH_3)_2$	$-CONH_2$	H	Cl	490.5	490
132	X	R	$-CH(CH_3)_2$	H	H	F	414.5	415
134	Z	S	$-CH_2OH$	H	H	F	402.4	403

5

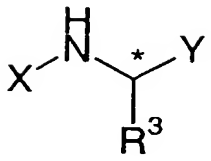
Table 5



Description No.	X	Y	R^3	Z	Stereochem. at position (*)
1	Fmoc	H	$-CH_2CH(CH_3)_2$	O	R
2	Fmoc	H	$-CH_2CH(CH_3)_2$	H_2	R
3	H	H	$-CH_2CH(CH_3)_2$	H_2	R
6	Fmoc	H	$-(CH_2)_4NHCO_2tBu$	H_2	R
7	H	H	$-(CH_2)_4NHCO_2tBu$	H_2	R
10	Boc	H	$-CO_2Et$	H_2	RS
11	Fmoc	H	$-CH_2CO_2tBu$	O	R
12	H	H	$-CH_2CO_2tBu$	O	R
13	H	H	$-(CH_2)_2OH$	H_2	R
14	Fmoc	H	$-(CH_2)_2SMe$	O	R
15	H	H	$-(CH_2)_2SMe$	O	R
16	H	H	$-(CH_2)_2SMe$	H_2	R
19	fmoc	H	$-CH_2CO_2tBu$	H_2	R/S (2:1)
20	fmoc	H	$-CH_2CO_2H$	H_2	R/S (2:1)
21	Fmoc	H	$-CH_2CO_2iBu$	H_2	R/S (2:1)
22	H	H	$-CH_2CO_2iBu$	H_2	R/S (2:1)
23	Fmoc	H	$-(CH_2)_2CO_2tBu$	O	R
24	Fmoc	H	$-(CH_2)_2CO_2H$	O	R
25	H	H	$-(CH_2)_2CO_2H$	O	R
26	H	H	$-(CH_2)_3OH$	H_2	R
28	Boc	H	$-(CH_2)_5NHCO_2tBu$	O	RS
29	H	H	$-(CH_2)_5NH_2$	O	RS
30	H	H	$-(CH_2)_5NH_2$	H_2	RS
32	Boc	H	$-CH_2Ph$	O	R
33	Boc	H	$-CH_2Ph$	H_2	R
34	H	H	$-CH_2Ph$	H_2	R
36	Boc	H	$-CH_2(4\text{-}NHCO_2tBu)Ph$	O	R

Description No.	X	Y	R^3	Z	Stereochem. at position (*)
37	Boc	H	$-CH_2(4-NHCO_2tBu)Ph$	H_2	R
38	H	H	$-CH_2(4-NH_2)Ph$	H_2	R
39	Boc	H	$-CH_2(4-NH_2)Ph$	H_2	R
40	Boc	H	$-CH_2(4-NHCOMe)Ph$	H_2	R
41	H	H	$-CH_2(4-NHCOMe)Ph$	H_2	R
42	H	H	$-CH_2(4-NHCOCF_3)Ph$	H_2	R
43	Fmoc	H	$-CH_2OtBu$	O	S
44	H	Me	$-CH_2OtBu$	H_2	S
45	2-Benzoxazolyl-	Me	$-CH_2OtBu$	H_2	S
46	H	H	$-CO_2H$	H_2	RS
47	2-Benzoxazolyl-	H	$-CO_2H$	H_2	RS
48	2-Benzoxazolyl-	H	$-(CH_2)_2CHO$	H_2	R

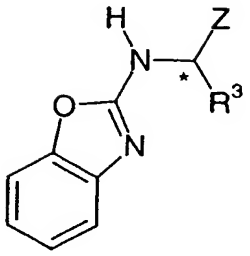
Table 6



Description No.	X	R^3	Y	Stereochem. at position (*)
4	Fmoc	$-(CH_2)_4NHCO_2tBu$	-CON(Me)OMe	R
5	Fmoc	$-(CH_2)_4NHCO_2tBu$	-CHO	R
8	Boc	$-CO_2Et$	$-CO_2H$	RS
9	Boc	$-CO_2Et$	-CON(Me)OMe	RS
17	Fmoc	$-CH_2CO_2tBu$	$-CH_2OH$	R
18	Fmoc	$-CH_2CO_2tBu$	-CHO	R
27	Boc	$-(CH_2)_5NHCO_2tBu$	$-CO_2H$	RS
31	Boc	$-CH_2Ph$	$-CO_2H$	R
35	Boc	$-CH_2(4-NHCO_2tBu)Ph$	$-CO_2H$	R
49	Boc	$-(CH_2)_5CO_2Et$	$-CO_2H$	RS
50	Boc	$-(CH_2)_5CO_2Et$	$-CH_2OH$	RS
51	H	$-(CH_2)_5CO_2Et$	$-CH_2OH$	RS
57	Boc	$-CH(CH_3)_2$	$-CH_2OH$	RS
58	Boc	$-CH(CH_3)_2$	$-CH_2OSO_2Me$	RS

5

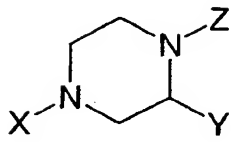
Table 7



Description No.	Z	R^3	Stereochem. at position (*)
52	$-CH_2OH$	$-(CH_2)_5CO_2Et$	RS
53	-CHO	$-(CH_2)_5CO_2Et$	RS
55	$-CH_2OH$	$-CH(CH_3)_2$	RS
56	-CHO	$-CH(CH_3)_2$	RS
66	-CO[1-(4- CO_2tBu)piperazinyl)	$-CH_2CO_2$tBu	R
67	$-CH_2$[1-(4- CO_2tBu)piperazinyl)	$-CH_2CO_2$tBu	R
68	$-CH_2$(1-piperazinyl)	$-CH_2CO_2H$	R

5

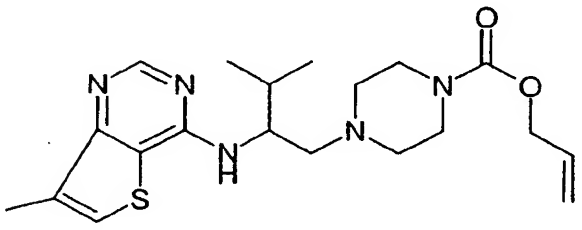
Table 8



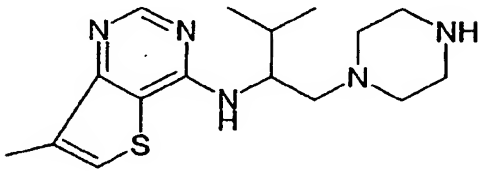
Description No.	X	Y	Z	Stereochemistry
54	H	$-CONH_2$	$-CH_2(3,4-Cl_2)Ph$	Racemic
59	$-CH_2CH(iPr)NHBoc$	H	H	Racemic
60	$-CH_2CH(iPr)NHBoc$	H	$-CO_2CH_2CH=CH_2$	Racemic
61	$-CH_2CH(iPr)NH_2$	H	$-CO_2CH_2CH=CH_2$	Racemic
64	$-COCH(CH_2OtBu)NHCO_2CH_2Ph$	H	Boc	(S)-enantiomer
65	$-COCH(CH_2OtBu)NH_2$	H	Boc	(S)- enantiomer

Table 9

(Structures of Descriptions 62 and 63)



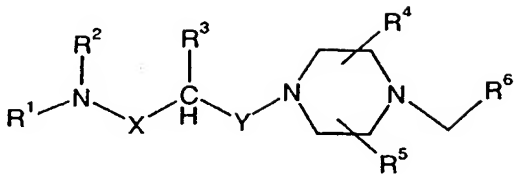
Description 62



Description 63

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 represents substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-8}cycloalkyl;

X and Y each independently represent a bond or $-(CH_2)_a-$, with the proviso that X and Y do not both represent a bond;

a represents 1 or 2;

R^3 represents C_{1-6}alkyl, C_{2-6}alkenyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, C_{3-8}cycloalkyl, $-CO_2R^7$, or $-CONR^7R^8$ wherein said C_{1-6}alkyl, C_{2-6}alkenyl, and C_{3-8}cycloalkyl groups may independently be either unsubstituted or substituted by one or more groups selected from $-NHSO_2R^7$, $-OCOR^7$, $-OR^7$, $-NR^7R^8$, $-NR^7COR^8$, $-NR^7CO_2R^8$, $-CO_2R^7$, $-CONR^7R^8$, $-NHCONR^7R^8$, $-SO_2NR^7R^8$, $-NR^7SO_2R^8$, $-O(CO)NR^7R^8$, $-S(O)_nR^7$, $-NHSO_2NR^7R^8$, -CN, $-NHC(=NR^{11})NR^7R^8$, C_{3-8} cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, or J groups;

n represents an integer from 0 to 2;

R^4 and R^5 each independently represent hydrogen, C_{1-6}alkyl, $-CO_2R^9$, $-CONR^9R^{10}$, oxo, or $-CH_2OR^9$;

R^6 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;

R^7 and R^8 each independently represent hydrogen, aryl, heteroaryl, C_{1-6}alkyl, or C_{3-8}cycloalkyl; wherein said C_{1-6}alkyl, or C_{3-8}cycloalkyl groups may be either unsubstituted or substituted by one or more of $-OR^{12}$, $-NR^{12}R^{13}$, $-CO_2R^{12}$, $-CONR^{12}R^{13}$, $-NHCONR^{12}R^{13}$, or aryl; alternatively R^7 and R^8 together represent a group $-(CH_2)_b-Z-(CH_2)_c-$;

b represents an integer from 0 to 4;

c represents an integer from 0 to 4;

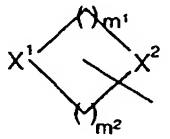
b + c is 3, 4, or 5;

R^9, R^{10}, and R^{11} may each independently represent hydrogen or C_{1-6} alkyl;

R^{12} and R^{13} may each independently represent hydrogen or C_{1-6} alkyl, wherein said C_{1-6} alkyl group may be either unsubstituted or substituted by $-OR^{14}$;

R^{14} represents hydrogen or C_{1-6} alkyl;

J represents a moiety of formula (K)



(K)

wherein;

X^1 represents oxygen, $-NR^{10}$, or sulphur;

X^2 represents CH_2, oxygen, $-NR^{10}$, or sulphur;

with the provisos that;

when moiety (K) is linked to the residue of the compound of formula (I) through an X^1 group, then X^1 represents N,

and when moiety (K) is linked to the residue of the compound of formula (I) through an X^2 group, then X^2 represents N or CH;

m^1 represents an integer from 1 to 3, m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5;

and wherein the moiety of formula (K) may be either unsubstituted or substituted by one or more of C_{1-6}alkyl, $-CONR^{12}R^{13}$, $-CO_2R^{12}$, or oxo;

Z represents oxygen, $-NR^{12}$, sulphur, or a methylene group, which methylene group may be either unsubstituted or substituted by a $-CO_2R^7$ or $-CONR^7R^8$ group;

and salts and solvates thereof;

with the proviso that N-[1-methyl-2-(4-benzylpiperazino)ethyl]aniline is excluded.

2. A compound according to claim 1 wherein R^1 is unsubstituted benzoxazolyl.

3. A compound according to any one of claims 1 to 2 wherein R^2 is hydrogen.

4. A compound according to any one of claims 1 to 3 wherein R^3 is selected from the group consisting of $-(CH_2)_2CO_2H$, $-CH_2(4\text{-}OH)Ph$, $-CH_2(4\text{-imidazolyl})$, $-(CH_2)_2CO(4\text{-morpholinyl})$, $-(CH_2)_2CONMe_2$, $-(CH_2)_2CONHCH_2CONH_2$.

5. A compound according to any one of claims 1 to 3 wherein R^3 is $-(CH_2)_2CO_2H$.

6. A compound according to any one of claims 1 to 5 wherein R^4 is hydrogen or $-CONR^7R^8$.

7. A compound according to any one of claims 1 to 5 wherein R^4 is hydrogen.

8. A compound according to any one of claims 1 to 7 wherein R^5 is hydrogen, C_{1-6}alkyl for example methyl, or $-CONR^7R^8$ for example amido.

9. A compound according to any one of claims 1 to 7 wherein R^5 is hydrogen.

10. A compound according to any one of claims 1 to 9 wherein R^6 is phenyl substituted with chloro.

11. A compound according to any one of claims 1 to 9 wherein R^6 is 3,4-dichlorophenyl.

12. A compound according to any one of claims 1 to 11 wherein R^7 is unsubstituted or substituted C_{1-6}alkyl, hydrogen, or unsubstituted or substituted aryl.

13. A compound according to any one of claims 1 to 12 wherein R^8 is unsubstituted or substituted C_{1-6}alkyl, hydrogen, or unsubstituted or substituted aryl.

14. A compound according to any one of claims 1 to 11 wherein R^7 and R^8 together represent a group $-(CH_2)_b$-Z-$(CH_2)_c$-.

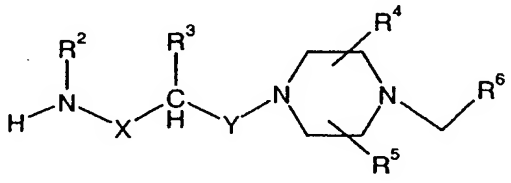
15. A compound according to any one of claims 1 to 14 wherein b is 0 or 2 and c is 2 or 3, provided that when b is 0 then Z is unsubstituted or substituted methylene.

16. A compound according to any one of claims 1 to 15 selected from Examples 58, 59, 62, 84, 93, and 94.

17. A compound according to any one of claims 1 to 16 which is Example 58.

18. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

Reacting a compound of formula (II)



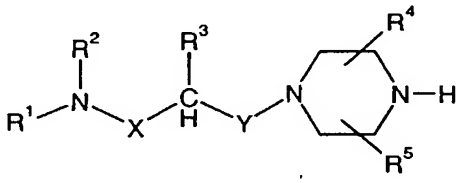
(II)

wherein;

R^2, R^3, R^4, R^5, R^6, X and Y are as defined in formula (I) in claim 1, with a compound of formula R^1-L^1, wherein R^1 is as defined in formula (I) in claim 1, and L^1 represents a leaving group, suitably a halogen atom, such as chlorine, , and optionally removing any necessary protecting group.

19. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

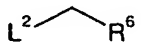
Reacting a compound of formula (III)



(III)

wherein;

R^1, R^2, R^3, R^4, R^5, X and Y are as defined in claim 1, with a compound of formula (IV)

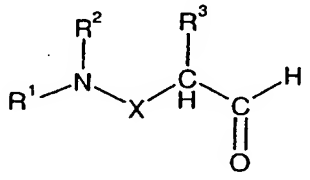


(IV)

wherein;

R^6 is as defined in claim 1 and L^2 represents a leaving group, suitably a halogen atom, such as bromine, and optionally removing any necessary protecting group.

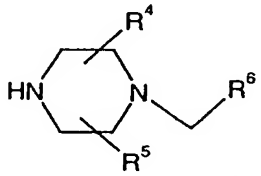
20. A process for preparing a compound of formula (I) as defined in claim1 in which Y represents $-CH_2-$ which process comprises:
Reacting a compound of formula (V)



(V)

wherein;

R^1, R^2, R^3 and X are as defined in formula (I) in claim 1, with a compound of formula (VI)

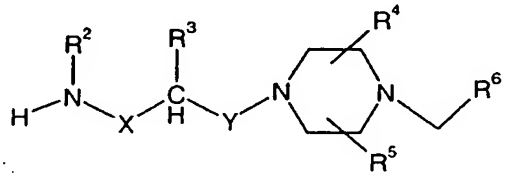


(VI)

wherein;

R^4, R^5 and R^6 are as defined in formula (I) in claim 1, followed by reduction of the resultant intermediate *in situ*, and optionally removing any necessary protecting group.

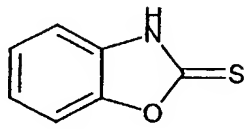
21. A process for preparing a compound of formula (I) as defined in claim 1 in which R^1 represents either unsubstituted or substituted 1,3-benzoxazol-2-yl which process comprises:
Reacting a compound of formula (II)



(II)

wherein;

R^2, R^3, R^4, R^5, R^6, X and Y are as defined in formula (I) in claim 1, with a compound of formula (VII)



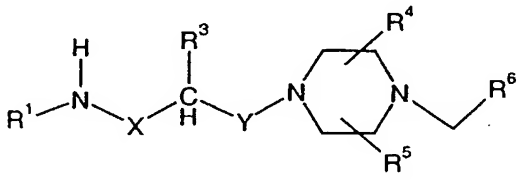
(VII)

wherein;

compounds of formula (VII) may be either unsubstituted or substituted with one or more substituents defined in claim 1 as being suitable for R^1, and optionally removing any necessary protecting group.

22. A process for preparing a compound of formula (I) as defined in claim 1 in which R^2 is other than hydrogen which process comprises:

Reacting a compound of formula (I) in which R^2 represents hydrogen i.e. a compound of formula (Ia)



(Ia)

wherein;

R^1, R^3, R^4, R^5, R^6, X and Y are as defined in formula (I) in claim 1, with a compound of formula R^{2a}-L^3, wherein R^{2a} is C_{1-6} alkyl or C_{3-8} cycloalkyl, and L^3 represents a leaving group, suitably a halogen atom such as iodine, and optionally removing any necessary protecting group.

23. A process for the preparation of a compound of formula (I) as defined in claim 1, which process comprises preparing a compound of formula (I) as defined in claim 1 from another compound of formula (I) as defined in claim 1, and optionally removing any necessary protecting group.

24. A compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, for use as an active therapeutic agent.

25. A compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions.

26. Use of a compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of patients with inflammatory conditions.

27. A method for the treatment of a human or animal subject with an inflammatory condition, which method comprises administering an effective amount of a compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof.

28. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

INTERNATIONAL SEARCH REPORT

Internati plication No
PCT/GB 03/00583

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/58 C07D413/12 C07D495/04 C07D235/30 C07D241/44
C07D239/48 C07D487/04 A61K31/495 A61P29/00
//(C07D413/12,263:00,263:00),(C07D413/12,263:00,233:00),
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 066484 A (LANGLOIS XAVIER JEAN MICHEL ;BAKKER MARGARETHA HENRICA MARI (BE);) 29 August 2002 (2002-08-29) example 26 ---	1,3,6-9
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2003	11/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bakboord, J

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INTERNATIONAL SEARCH REPORT

Internati plication No
PCT/GB 03/00583

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D413/12,263:00,257:00),(C07D495/04,333:00,235:00), (C07D487/04,239:00,231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bakboord, J

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INTERNATIONAL SEARCH REPORT

Internatic plication No
PCT/GB 03/00583

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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PCT/GB 03/00583

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